ARCHIVES OF PATHOLOGY

VOLUME 18 NOVEMBER 1934 NUMBER 5

EXPERIMENTAL STUDIES ON HUMAN AND PRIMATE SPECIES OF STRONGYLOIDES

III. THE FECUNDITY OF STRONGYLOIDES FEMALES OF THE PARASITIC GENERATION

ERNEST CARROLL FAUST, PH.D.

JOSEPH W. WELLS, B.S.

CORINE ADAMS, M.S.

AND

TED D. BEACH, M.S.

NEW ORLEANS

In our earlier studies on experimental Strongyloides infections in man, in dogs and in several species of monkeys, we were particularly concerned (1) with the type of strain as it developed in culture and as it was subinoculated successively from one host to the next,[1] and (2) with the consecutive stages in the development of the parasitic generation, including both females and males.[2] It soon became evident that the strains utilized manifested marked variability and instability in type. There appeared to be some evidence of correlation on the one hand between indirect strains and fertilized eggs of the parasitic worms, and, on the other, between direct strains and unfertilized eggs. While this correlation was not a matter of direct experimental proof, evidence favoring this view was submitted for consideration.[2]

The problem was complicated by other factors. In dogs of the same size, weight and age, fed the same rations, inocula of filariform larvae from the same cultures in similar amounts, introduced by the same route, resulted in infections which produced different daily and average yields of rhabditiform larvae in the evacuated stools. Furthermore, autopsy on the experimental hosts revealed a difference in the egg-producing capacity of the parasitic females. After several months of infection some worms were maintaining a high productivity; others were producing a small number of eggs, and still others were apparently completely unproductive.

Contribution from the Parasitology Laboratory, Department of Tropical Medicine, Tulane University of Louisiana.

This investigation was supported by a grant from the Committee on Scientific Research of the American Medical Association.

1. Faust, E. C., and Kagy, E. S.: Am. J. Trop. Med. **13**:47, 1932.
2. Faust, E. C.: Am. J. Hyg. **18**:114, 1933.

In an attempt to discover the basis for these differences in the fecundity of parasitic females in human and nonhuman strains of Strongyloides, series of controlled experimental infections were undertaken.[3]

MATERIAL AND TECHNIC

The data presented in this communication were obtained from a study of seventeen pups (from 3 to 6 months old at the time of inoculation) inoculated with human strains of Strongyloides stercoralis, and one 5 year old Pithecus rhesus, inoculated with a chimpanzee strain, morphologically and physiologically identical with human strains (indirect type) of S. stercoralis. In the canine series, previous to inoculation the animals were devocalized, treated with tetrachlorethylene for the eradication of hookworms and tested by intensive fecal examination and culture to make sure, so far as antemortem tests could indicate, that they did not harbor Strongyloides. Seven animals (nos. 42 [second inoculation], 43, 45, 47, 48 [twice], 56 and 59) were inoculated by the oral route; eight (nos. 41, 42 [first inoculation], 57, 60, 61, 62, 63 and 64), by the abdominal cutaneous route, and three (nos. 50, 54 and 58), by the intracecal route. Except for nos. 56, 57, 58 and 59, in which second generation (indirect type) filariform larvae were used, all the animals were inoculated with first generation (direct type) filariform larvae (f_1 or F_1). In the case of dog 47 the inoculation was obtained after passage through dog 45, and in dog 59, larvae obtained from the feces of dog 48 were used as the inoculum. All the remaining dogs were inoculated with larvae obtained directly from cultures of human stools. Five human strains were utilized (strain M, six animals; strain O, six animals; strain P, two animals; strain Q, four animals, and strain R, one animal; two duplicate inoculations were made). A fecal examination of each animal was made daily for the period from two weeks before inoculation until autopsy.

As soon as the animal showed evidences of harboring the organism (or, in certain exceptions, somewhat later) the fresh daily fecal evacuation was weighed; a 5 Gm. portion was carefully screened through wire gauze and concentrated, and the total number of larvae (or eggs) in the sample were counted. In this way the total daily yield of the progeny was calculated, with an estimated error usually not over 10 per cent. Although this count of the total number of larvae or eggs present in the 5 Gm. sample was exceedingly tedious, it frequently demonstrated their presence when three ordinary fecal samplings were negative.

The greatest difficulty arose in detecting dead and degenerate larvae in the stool. It was found necessary to dilute the concentrate sufficiently so that fragments of larvae were not obscured by débris. Because of the percentage of dead and degenerating larvae in freshly passed feces (of man and dogs), ranging at various times from 5 to 90 per cent, it was found that Sandground's technic[4] for culturing the progeny was entirely unreliable in providing a basis for estimating the total production of the parasitic females. On a few occasions the feces were found contaminated with Rhabditis larvae from the perianal hairs, even though the animals and their cages were regularly scrubbed with a strong solution of cresol. When such contaminations occurred the counts had to be discontinued for two or three days.

---

3. Faust, E. C.; Wells, J. W.; Adams, C., and Beach, T. D.: Proc. Soc. Exper. Biol. & Med. **31**:1041, 1934.

4. Sandground, J. H.: Am. J. Hyg. **6**:337, 1926; **8**:507, 1928.

All the animals in the series were killed. The following technic was carried out at autopsy: On opening the abdominal cavity the gastro-intestinal tract was tied off above the cardiac sphincter and at the anus and removed as a complete viscus. Similarly, above the diaphragm, the lungs, bronchi, trachea, glottis and esophagus were removed en masse. The stomach and intestines were opened from above, and the work was carried on distalward. The contents of the lumen of each level were first washed out into physiologic solution of sodium chloride; following this, scrapings were made from the mucosal surface successively deeper and deeper down to the muscular coats. (Experience has shown that the worms rarely penetrated below the muscularis mucosae). Approximate estimates of the numbers of eggs and larvae and exact counts of adult worms were made for successive levels of the entire lumen and of the mucous and submucous coats of the entire stomach and intestines, so that the total number of parasitic females was believed to have been discovered. The trachea and bronchi were opened from above downward into the bronchioles. Washings and scrapings were made along the entire respiratory tree and examined microscopically. Scrapings were then made from representative sections of the lungs following which the lungs were chopped up, left in physiologic solution of sodium chloride in the electric ice-box overnight, squeezed and strained out the next morning, and the semiliquid yield centrifugated. The centrifugate was then completely examined under the microscope for adult worms and larvae. The esophagus was washed and scraped in a similar manner. When females were recovered, a careful study was made of their condition—whether active, semiactive or dead, whether mature or immature—and more particularly efforts were made to discover indications of continued or reduced productivity in mature females, as determined by eggs or larvae in utero and in the immediately adjacent tissues of the host.

PRESENTATION OF DATA

A. Human Infections in Dogs.—The canine series was divided into three subseries: (1) those which were negative for parasitic females at autopsy; (2) those with relatively light infections (200 or less females per animal), and (3) those with relatively heavy infections (more than 200 females per animal).

1. *Animals Showing No Evidence of Organisms at Autopsy.*—Dog. 54: The animal was inoculated intracecally with 250 active f_1 larvae, strain O (six day culture). Organisms were found only once, one hundred and forty-three days after inoculation. The animal was killed on the two hundred and third day. No Strongyloides, adults or larvae, were found on thorough examination of the organs, except one dead filariform larva from the right lung (believed to have been a contamination, but possibly the progeny of a female undetected in the postmortem search).

Dog 42: The animal was inoculated on the skin of the abdomen with 5,000 active F_1 larvae, strain M (three day culture). The prepatent period was sixteen days. The animal showed Strongyloides five times during the next fifty-five days. It was reinoculated on the fifty-fifth day with 500 f_1 larvae (strain O, one day culture) in aqueous suspension introduced into the buccal cavity. The prepatent period of the second infection was twenty-four days, as indicated by the large number of larvae which appeared for the first time at the end of that period. Larvae were again found twice within the next six months. The animal was killed nine months after the original inoculation. The postmortem search for Strongyloides gave negative results.

2. *Animals with Relatively Light Infection.*—Dog 45: The animal was inoculated orally with 250 f_1 larvae (five day culture, strain M). The prepatent period was sixteen days. The animal showed a slight evidence of infection on five isolated days within the next one hundred and thirty days. It was killed on the one hundred and thirty-first day. Forty-four nonfecund parasitic females were found as follows: duodenum, 10; jejunum, 24; ileum, 3; concentrate of intestinal washings, 7. The lungs were normal. An example of the females obtained from the intestine is shown in figure 1. Uterine cords had developed but had not yet formed hollow tubules; no eggs were found. All the body characters were indicative of a young adolescent parasitic female. The case is interpreted as one in which the original infection had died out and a more recent

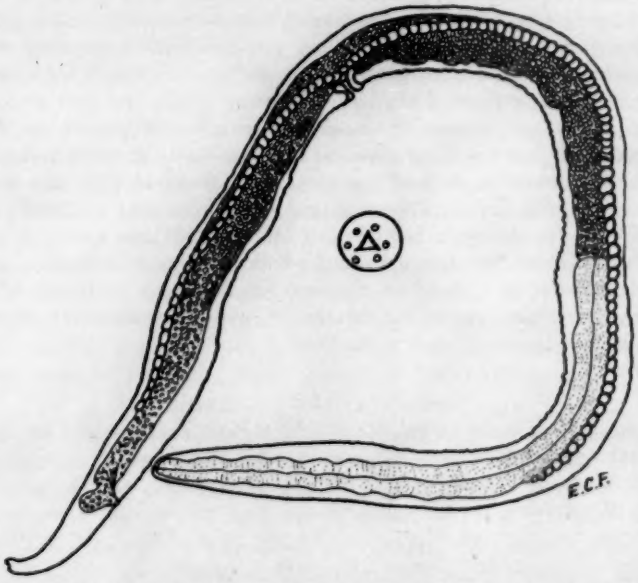


Fig. 1.—Adolescent female S. stercoralis removed from deep scrapings of the duodenum of dog 45, two hours after the host was killed on the one hundred and thirty-first day after inoculation. The midintestine and rectum of the parasites are filled with granular material. The vulva is readily distinguished on the ventral (incurved) side, just behind the middle of the worm. The two horns of the uterus, with their oviduct-ovarian continuations, are still solid cords and have not yet become hollow tubules. In the center of the illustration is a head-on diagrammatic representation of the buccal opening, surrounded by six oral papillae. Drawing by means of camera lucida; × 200.

(hyperinfective?) group of females had not yet reached maturity. All the worms were apparently in the same stage of development.

Dog 43: This dog was inoculated orally with 1,000 f_1 larvae (strain O, one day culture). The prepatent period was eighteen days. The results of examination were positive on six isolated occasions during eighteen days. The animal was killed on the one hundred and sixty-fifth day. Twenty-seven females were found as follows: duodenum, 22; jejunum, 4; concentrate of intestinal wash-

ings, 1. Only 3 worms contained eggs, 2 each. No eggs or larvae were found in the concentrates of the lumens or in the scrapings from tissue. The lungs were normal. The yield of females constituted only 2.7 per cent of the number of filariform larvae in the inoculum.

Dog 64: The animal was inoculated by the abdominal cutaneous route with 1,500 f_1 larvae from a one day culture (strain Q). The prepatent period was eleven days. The calculated total numbers of larvae in evacuated feces for the next thirty-one days were as follows: 16; 57; 1,224; 80; 24; —; 0; 0; 78; 0; 216; 0; 0; —; 14; 0; 0; 0; 0; 0; 0; 10; —; 0; 0; 0; —; 0; 0; 0; 0.[5] The animal was killed on the forty-second day after inoculation. One hundred and sixty-six female worms were recovered as follows: duodenum, 73; jejunum, 77; ileum, 3; concentrate of intestinal washings, 13. Less than 10 per cent of the worms contained eggs (from 1 to 3 each). Most of the worms were encapsulated. No larvae were seen in the tissues or concentrates. The lungs were normal. The yield of parasitic females recovered was 11 per cent of the larvae used in the inoculum.

Dog 48: The animal was inoculated orally with 1,500 F_1 larvae (one day culture, strain M). The prepatent period was thirteen days. Larvae were found again in stools only on two succeeding days after the period of incubation. On the nineteenth day the animal was reinoculated by mouth with 500 f_1 (four day culture, strain O). The prepatent period of the second strain was fourteen days. For two weeks thereafter large numbers of larvae were recovered from the stools. After three months 5 Gm. samples of feces were consistently negative. The animal was killed on the one hundred and fortieth day after the original inoculation. One hundred and forty-four female worms were recovered from the following levels of the intestinal tract: duodenum, 69; jejunum, 71; ileum, 1; concentrate of intestinal washings, 3; lungs, 1 female and 1 preadolescent male worm. Except for a single specimen which had a few eggs in utero, all the females were active but were apparently nonfecund. No eggs or larvae were found in the tissues.

Dog 56: It was inoculated orally with 1,000 f_2 larvae (four day culture, strain P). The prepatent period was thirteen days. Larvae were recovered again only on four isolated occasions during the next thirty-six days. The animal was killed one hundred and ninety days after inoculation. Only 3 parasitic female worms were recovered as follows: duodenum, 2; ileum, 1. They were all encapsulated, and none of them contained eggs. No eggs or larvae were found in the surrounding tissues. However, two viable filariform larvae of Strongyloides were recovered from lung concentrates.

Dog 57: The animal was inoculated by the abdominal cutaneous route with 500 f_2 larvae (three day culture, strain O). The feces never showed the presence of the organism. The animal was killed six and a half months after inoculation. Six nonfecund encapsulated female worms were recovered as follows: duodenum, 2 (each with 1 degenerating egg in utero); jejunum, 2; concentrate of intestinal washings, 2. The lungs were normal.

Dog. 47: This dog was inoculated orally with 200 F_2 larvae (one day culture, strain M). The prepatent period was fifteen days. The total numbers of calcu-

5. A dash indicates that no stools were passed.

lated larvae in evacuated feces for forty-eight consecutive days were as follows: 0; 25; 0; 0; 0; 12; 0; 152; 95; 0; 0; 0; 0; 0; 0; —; 25; 0; 0; 0; 11; 0; 15; 0; 0; 19; 0; —; 0; —; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0; 0.[5] The animal was killed six and one-half months after inoculation. Six female worms were recovered as follows: duodenum, 3; concentrate of intestinal washings, 3. One unencapsulated female contained 3 apparently fertile eggs in utero; the others (all encapsulated) were nonfecund. No eggs or larvae were found in the tissues of the intestinal wall.

3. *Animals with Relatively Heavy Infection.*—Dog 61: The animal was inoculated by the abdominal cutaneous route with 1,500 f_1 larvae (four day culture, strain Q). The prepatent period was eleven days. The number of larvae calculated to have been passed in evacuated feces for seventy-six consecutive days was as follows: 253; 42,728; 202; 4,715; 6,094; 3,365; 1,265; 3,078; 32,929; 1,823; 25,519; —; 5,531; —; 12,070; 62,496; 3,504; 14,033; 1,760; 6,282; 12,642; 2,230; 33,886; 5,876; 122,262; 102,500; 78,019; 108,720; 61,700; 95,900; 63,900; 80,700; 97,950; 114,150; 33,750; 4,500; 44,800; 6,160; 19,650; 53,550; 21,450; 38,850; 25,600; 20,400; 21,450; 18,150; 5,000; 15,150; 10,950; 5,000; 3,300; 2,800; 4,200; 1,700; 14,250; 6,300; 2,800; 1,500; 2,860; 3,500; 1,500; 1,700; 3,500; 2,400; 600; 2,550; 1,100; 0; 0; 0; 0; 600; 800; 150; 300.[5] The animal was killed on the eighty-fifth day after inoculation. Six hundred and eight female worms were recovered as follows: duodenum, 91; jejunum, 392; ileum, 63; concentrate of intestinal washings, 62. Only 1 egg and no larvae were found in the abdominal viscera examined; the egg was lodged in the tissues; all the females were nonfecund and encapsulated. The thoracic viscera were normal.

Dog 59: This dog was inoculated orally with 2,000 f_2 larvae (six day culture of strain O, through dog 48). The prepatent period was twelve days. The numbers of larvae calculated to have been passed in the evacuated stool for thirty-seven consecutive days after the prepatent period were as follows: 41; 3,758; 6,050; 9,786; 396; 1,152; 8,597; 8,864; 1,061; 8,659; 1,031; 16,541; 2,136; 4,598; 2,494; 19,734; 11,380; 12,833; —; 26,296; 2,659; 2,672; 5,930; 12,642; —; 7,912; 2,482; 10,512; 8,332; 2,150; 6,415; 644; 366; 3,481; 770; 785; 2,479.[5] The animal was killed on the forty-ninth day after inoculation. Seven hundred and eight female worms were recovered as follows: duodenum, 109; jejunum, 293; ileum, 171; concentrate of intestinal washings, 135. Thirty-seven rh_1 larvae were found in the pyloric wall of the stomach, but no adult worms were discovered there. The reaction of gastric juices was weakly basic. The number of larvae seen in the intestine proper was somewhat smaller than the yield of females. The females recovered from scrapings of living tissue in the duodenum and upper jejunum were deeply embedded in the mucosa. Some were surrounded by epithelial envelops. Only a few eggs were found in a small proportion of the females; most females were apparently postproductive. The thoracic viscera were normal.

Dog 41: The animal was inoculated by the abdominal cutaneous route with 2,000 f_1 larvae (four day culture, strain M). The prepatent period was fourteen days. The feces were strongly positive for four months following the first recovery of larvae. The calculated counts of larvae, based on weighed samples for eight days at the end of this period, were as follows: 7,779; 4,613; 12,305; 2,073; 5,904; 5,409; 3,155; 2,295. The animal was killed five months after inoculation. Eight hundred and forty-four female worms were recovered from the intestine as follows: duodenum, 318; jejunum, 374; ileum, 118; concentrate of intestinal washings, 34. The thoracic viscera were normal. The eggs in utero and both eggs and larvae in the tissues were numerous. There was no evidence of

greatly diminished fecundity in mature worms, although about 25 per cent were immature or had apparently just commenced to lay eggs.

Dog 60: It was inoculated by the abdominal cutaneous route with 750 f_1 larvae (one day culture, strain Q). The prepatent period was five days. The calculated total numbers of larvae for thirty-seven successive days following patency were as follows: 6; 51; 0; 39; 14; 0; 122; 0; 90; 7; 0; 41; 17; 0; 0; 10; 108; 0; 5; 0; 8; 0; 0; —; 0; 44; 48; 0; 241; 1; 125; 67; 32; 14; 65; 34; 88.[5] On the twenty-eighth day of this count one active parasitic female, containing two unembryonated eggs in utero, was recovered from the fecal concentrate. The dog was killed on the forty-first day after inoculation. Eight hundred and twenty-one female worms were recovered from the intestine as follows: duodenum, 186; jejunum, 500; ileum, 79; concentrate of intestinal washings, 56. One filariform Strongyloides larva was recovered from the left lung. The great majority of the females were postproductive, and some were surrounded by epithelial envelops.

Dog 50: The animal was inoculated intracecally with 100 f_1 larvae (strain M, passed through dog 41). The prepatent period was eleven days. Larvae were found occasionally in the feces during the next fifty days. The calculated numbers of larvae for the next six days (fifty-first to fifty-seventh day) were as follows: 624; 167; 20; 574; 638; 300. The animal was killed on the one hundred and twentieth day after inoculation. Two hundred and fourteen parasitic females were recovered as follows: duodenum, 71; jejunum, 104; ileum, 16; concentrate of intestinal washings, 25. The worms usually contained a few (rarely more than three) formed eggs in utero. Unformed or infertile eggs were frequently found in tissues immediately surrounding the females, along with smaller numbers of embryonating eggs. A few recovered females were in the adolescent stage. No worms were found in the lungs, but a few embryonating eggs were obtained from concentrates of each lung, apparently indicating the presence in each organ of at least one fertile female which had been overlooked. The data definitely indicate a hyperinfection, with a yield of adult females amounting to more than twice the number of f_1 larvae in the original inoculum.

Dog 62: This dog was inoculated by the abdominal cutaneous route with 2,000 f_1 larvae (strain Q). The prepatent period was thirteen days. The number of larvae on the day following the first recovery of larvae in stools was calculated to be 525. The animal was killed on the next day. Two hundred and forty-eight unencapsulated female worms were recorded from the intestine as follows: pylorus, 1; duodenum, 134; jejunum, 90; ileum, 4; concentrate of intestinal washings, 19. Eggs and motile rh_1 larvae were numerous at various levels of the bowel. The thoracic viscera were normal.

Dog 63: The animal was inoculated by the abdominal cutaneous route with 14,000 f_1 larvae (one day culture, strain R). The prepatent period was fourteen days. The daily computations of the total number of larvae in the feces for twenty-six days from the beginning of patency were as follows: 220; 0; 35; 54; 54; 0; 42; 52; 22; 0; 0; 0; 0; 0; 1; 934; 19; 0; 0; 0; 45; 0; 0; 0; 0; 0. The animal was killed on the day after the last count was made (forty-one days after inoculation). Four hundred and sixty-two female worms were recovered from the intestine as follows: duodenum, 112; jejunum, 303; ileum, 29; concentrate of intestinal washings, 18. Most of the worms contained only a few eggs in utero; some worms were already definitely postfunctional, as indicated by the complete absence of egg-forming material in the ovaries and by the transparent, glossy consistency of all their tissues and organs; the worms, however, were still alive. All these worms

were enveloped in an epithelial capsule. Tissues immediately surrounding the worms contained only a few eggs and larvae.

Dog 58: It was inoculated intracecally with 2,000 f_2 larvae (five day culture, strain P). The prepatent period was twelve days. The stools were positive daily for twelve days, later they were irregularly positive as shown by the routine smear method. Computations of the number of larvae, based on daily counts for seven days, beginning seventy days from the date of patency were as follows: 178; 102; 136; 138; 112; 34; 0. The animal was killed on the eighty-ninth day after inoculation. Two hundred and ten female worms were recovered from the intestine as follows: duodenum, 58; jejunum, 117; ileum, 24; concentrate of intestinal washings, 11. Nearly all these worms were enveloped in an epithelial capsule (fig. 2). Few eggs were present in utero or in the tissues of the host immediately surrounding the worms. Fewer larvae were found in the tissues. Only four worms were definitely found to be still productive. Most worms were postproductive, with the integument greatly contracted and the protoplasm transparent, although such worms became very active when removed to physiologic solution of sodium chloride. A small portion of the yield was diagnosed on morphologic characters as preadolescent or adolescent. The worms recovered were roughly grouped as follows: (1) preadolescent and adolescent females, 15 per cent; (2) productive females, 2 per cent, and (3) postproductive females, 83 per cent. The pulmonary tissues gave the following yield: left lung, 1 preadolescent female; right lung, 7 postfilariform larvae (sex undetermined).

B. Strongyloides in the Monkey.—This work was carried out on a five year old Pithecus rhesus, which had been under laboratory observation for four years and had never showed evidence of harboring Strongyloides during this period. The animal was inoculated orally with 24,000 f_2 larvae of a chimpanzee strain, which had been studied for four months previously in the original host as well as in a rhesus monkey and in a human volunteer. The strain was known to be a pure indirect type. The animal showed evidence of harboring the organism after a seventeen day period of incubation. The number of eggs and larvae in the stools gradually increased for the next month. After four months the calculated number per twenty-four hour sample amounted to about 1,000,000. During this period the monkey had a leukopenia (25 per cent) with marked eosinophilia (18.5 per cent). Daily examinations were continued for the next five months, but quantitative studies were not resumed until the end of that period, when counts indicated a greatly reduced first generation progeny, as demonstrated by the following total daily calculated output over a period of twenty-nine days: 3,480; 21,608; 10,250; 38,000; 13,150; 83,600; 38,350; 21,875; 12,800; 12,600; 26,800; 9,500; 36,400; 5,704; 22,800; 22,050; 36,800; 33,600; 38,800; 33,300; 22,000; 28,600; 33,920; 32,400; 32,200; 32,900; 23,700; 40,808, and 25,500. After a three week intermission another five week count showed about the same productive level, with comparable daily variations. Fourteen months after inoculation the average daily count became noticeably lower, as follows: 12,600; 12,000; 10,000; 1,350; 22,000; 18,000; 11,200; 20,700; 27,500, and 10,800.

The host was killed fourteen and a half months after inoculation. At autopsy 523 unencapsulated parasitic females were recovered from the following levels in the intestinal wall: pylorus, 1; duodenum, 376; jejunum, 110; ileum, 7; cecum, 1; concentrate of intestinal washings, 28. Large numbers of eggs were present in the lumen and in the immediate vicinity of the worms in the tissues. While eggs in utero indicated that practically all the parasitic females were still productive, the number of such eggs per female was small, usually only 2 or 3 and never over 10. No worms, eggs or larvae were found in the thoracic viscera.

The figures for the infection in the monkey show a maximum daily computed number of 1,000,000 progeny one hundred and thirty-eight days after inoculation; a marked reduction to an average level of 25,000 eggs, with considerable daily fluctuations, after ten months; a continued production of eggs at approximately this level for about three months, and a subsequent drop in the level to an average of 13,250. On the basis of parallel examinations of another rhesus monkey inoculated with this chimpanzee strain, it may be concluded that the fertility of the parasitic females would have ceased in the following two or three months, after which there would have been no further evidence from the feces of the presence of worms in the intestinal wall.

At the time the average daily output of first generation progeny was 25,000 the daily output per worm was calculated to be approximately 50; later it dropped to about 27. These figures, which are much greater than the maximum number of eggs in utero in the parasitic females at autopsy, indicate either that the production of eggs and parturition occurred considerably more frequently than once daily, or that the worms were much less productive at autopsy than they were during the periods when the counts were made. This question will be considered later.

GENERAL CONSIDERATIONS

A casual examination of the data which have been presented indicates that in Strongyloides infections in the experimental host processes are at work which involve both the parasite and the host. In the first place, our studies, like those of previous investigators, demonstrate that infection may be acquired either cutaneously or orally. In the latter case it may be temporarily assumed that the filariform larvae invade the venous blood stream via the buccal, pharyngeal and esophageal mucosa. Experimental proof of this assumption has been obtained by us and will be published elsewhere. In experimental animals both methods of inoculation are equally successful, although it is likely that in nature the cutaneous route is by far the more common. Furthermore, we have demonstrated that infection may be readily established by introducing larvae in the infective stage into the lumen of the large bowel. In this demonstration of how internal infection (hyperinfection) may occur, the greatest precautions were exercised to prevent any larvae returning through the anus from penetrating through the perianal skin, by keeping this area thoroughly saturated with a strong solution of iodine for several hours after the inoculum had been introduced into the cecum. Infections may therefore be established by three portals of entry: (1) the skin, (2) the pregastric mucosa and (3) the intracecal route.

One of us [2] has previously shown the successive stages in the development of the adult female and male parasitic Strongyloides, including

the filariform and postfilariform larvae, the preadolescent, adolescent and mature worms, and, later, the postfunctional and degenerate females. Evidence favors the view that females, if fertilized by the "ephemeral" males, are apparently impregnated in the adolescent stage, either in the bronchioles of the lungs or before they enter the intestinal mucosa. While the intestinal wall is the common habitat of adult worms, it has been shown that the bronchioles of the lungs are a suitable site for their complete development and that this focus may be a source of subsequent hyperinfection. Females may become mature and begin to produce eggs in the lungs as early as the third day after inoculation; in the intestine they may produce eggs as late as the twenty-seventh day.

Females may begin to lay eggs before actually penetrating into the intestinal mucosa, but this is not common. In a previous series of experiments some of the canine hosts were killed between the fifth and the ninth day after inoculation. At this stage of the infection the animal frequently had a prodromal diarrhea. The duodenum and jejunum, when opened, were usually hyperemic and hemorrhagic. Surface scrapings of the mucosa ordinarily yielded a film of mucus in which there were many adolescent and maturing females and, less commonly, adolescent and mature males. Free eggs and rhabditiform larvae were not numerous in the film (not over 2 or 3 per female worm). A few developing eggs were always present in each uterine arm of young mature worms. This condition preceded by one or two days the appearance of rhabditiform larvae (less frequently of eggs) in the fecal dejecta. From that time on for several days it was found that the females penetrated more deeply into the mucosa, so that, when the animal was killed, successively deeper scrapings of this layer were required to obtain a maximum yield of adult females and larvae.

When the females had become well established in the mucosa of the intestinal wall, parturition rapidly rose to a maximum; then, after a period of days, weeks or months, it descended to a level which was much lower, but still greatly in excess of the total number of uterine eggs in the female worms. Later this production of eggs was gradually reduced to a lower and lower level, and finally it ceased. Although individual counts of progeny produced by the mother worms seldom coincided in any two canine hosts, under conditions as comparable as it was possible to obtain, the sequence of events was essentially the same. In some animals the period of egg production was apparently limited to weeks; in others, to months. Since such discrepancies existed in animals inoculated with homologous as well as with heterologous strains, it is suggested that the determining factor is probably a reaction of the tissue of the host to the worm and is not intrinsic in the worm itself. In the infection of the monkey, after declining from a high maximum, the

moderate level of egg production was maintained over a period of many months, but later it showed a definite evidence of diminution.

The canine series in this study has been presented more or less in reverse order to the fecundity of the worms (see Presentation of Data, *A*). Dogs 54 and 42 did not show evidences of Strongyloides at autopsy; dogs 45, 56, 57 and 61 had only nonfecund females; dogs 43, 64, 48, 47, 59, 60, 50, 63 and 58 yielded females which were mostly nonfecund, while dogs 41 and 62 harbored worms which showed evidence of continued fecundity. The productivity of these females was not correlated with the strain of the organism, nor was it always related to the length of the infection within the host, although the general tendency was a definite decline in the production of eggs after a period of months. Taken as a whole, the productive period of human Strongyloides in dogs is relatively short, a matter of months, as contrasted with a period presumably of years in man, so that the complete life cycle is considerably abbreviated. This has both its advantage and its disadvantage: it is of advantage in demonstrating the complete picture of development and egg production in a relatively short time, but of disadvantage in making a direct comparison with human infections more difficult.

The percentage of female worms recovered at autopsy, as compared with the number of filariform larvae present in the inoculum, varied enormously. When dogs 54 and 42, from which no worms were recovered, are omitted, the yield ranged from 0.3 per cent (dog 56) to considerably over 100 per cent (dog 60, 109.5 per cent; dog 50, 214 per cent). The majority, however, varied from 10 to 40 per cent. Since experience has shown that a large number of filariform larvae are filtered out in the skin when the inoculum is applied to this portal of entry,[6] a yield of parasitic females amounting to between 10 and 20 per cent of the filariform larvae used in cutaneous inoculations is considered to be satisfactory. This series of experiments indicates that oral or intracecal administration of the inoculum gives results comparable to those obtained by cutaneous inoculation. In each series there are cases with more than a 20 per cent yield (cutaneous route, 3, 42.4 per cent of animals employed; oral route, 1, 16.6 per cent, and intracecal route, 1, 50 per cent). Since the parasitic females recovered at autopsy represent the minimum and not the maximum number of females which actually matured, and since allowance must also be made for parasitic males, any excess of worms above 20 per cent of the larvae in the inoculum requires analysis. Certainly yields above 100 per cent demand a careful scrutiny. It is not likely that any considerable error (10 per cent or more) resulted from underestimating the number of larvae in

6. Stumberg, J. E.: Am. J. Hyg. **15**:186, 1932. Faust.[2]

the inoculum, since two measured samplings of the larvae in each inoculum were carefully counted immediately before the inoculation was undertaken. A portion of such larvae was believed to consist of potential males, and was, therefore, not accounted for in the counts at autopsy made any considerable length of time after the prepatent period.[2] Thus in five animals in the series the actual yield of parasitic females at autopsy is far in excess of expectations. In our opinion this can be accounted for in one way only, namely by internal infection (hyperinfection). Information supporting this view is furnished from two sources. In the case of dogs 50 (intracecal inoculation) and 47 (oral route) on at least one occasion active dwarf filariform larvae (f_1) were recovered from the freshly passed stool which still retained the body warmth of the host. In the female worms recovered from dogs 41 and 58 (on which autopsy was done respectively five months and eighty-nine days after inoculation) there was in each case a definite evidence of premature or recently matured female worms (dog 41, 25 per cent of the yield; dog 58, 15 per cent of the yield). In dogs 50 and 47 there was a clue as to the method of internal infection (i. e., dwarf filariform larvae within the bowel in a favorable position to invade the intestinal mucosa). That this method is possible is well illustrated by the positive results of intracecal inoculation of dogs 50 and 58, as well as of other dogs not included in this series. In dogs 41 and 58 there was evidence of recent development of female parasites. While actual proof was not obtained in the case of other animals in which an unexpectedly high yield of parasitic females was obtained at autopsy, it is logical to believe that in the case of those animals, too, the number of organisms was increased by the mechanism of internal infection.

In the section on technic we have referred to the difficulties encountered in obtaining data on the daily productivity of the female worms from examination of the feces. Three fecal smears frequently failed to reveal a single egg or larva. For this reason as well as in order to obtain a quantitative estimate of the daily discharge of eggs in the feces, it was soon discovered that another technic must be employed. Cultures of the material were most unsatisfactory, not only because some of the larvae died in the culture, but more particularly because many larvae were frequently dead when the stools were passed. Even in samplings taken from the upper colon and cecum, at times as many as 80 per cent of the larvae were nonviable. It was, therefore, necessary to make daily counts of weighed samples; these were washed, concentrated and then spread out sufficiently thin on fecal slides so that no worm or fragment of a worm was overlooked in the count. From these counts the total daily discharge of progeny in the feces was reckoned, since the weight of the total fecal discharge was obtained as a routine. We believe, there-

fore, that our calculations are reasonably accurate, although they are minimum rather than total, since it is not unlikely that some larvae had completely disintegrated within the bowel, while there is concrete evidence indicating that in two cases some rhabditiform larvae transformed into the filariform stage within the bowel and may have penetrated into the intestinal mucosa. Nevertheless, we believe that counts of larvae discharged in the feces, no matter how accurate, constitute an unsatisfactory criterion of the daily output of eggs or larvae by the parasitic female. Our conclusions are based on the following grounds:

In the first place, although each dog and the monkey in our series usually had a daily fecal discharge, there were days when no defecation occurred. More commonly the stools were fairly regular and equal in amount, but the numbers of larvae expelled were inconstant. Any variation in larval counts, such as that for dog 59, indicates the irregularity of such discharges of larval progeny. We have been unable to find any intrinsic or extrinsic evidence in the levels of the small intestine, where the majority of the females reside, which explains this irregularity satisfactorily. Only one fact bearing on the situation is known, namely, that the average daily output of larvae (or eggs), as measured either by those counted in the stools or by those present in the lumen of the duodenum and upper jejunum, is far in excess of the number of eggs present in the uteri of fecund females, even at the peak of egg production. By the time the females have become parturient they are usually well embedded in the mucosa, with their vulvae in such a position that eggs are shed into the deeper levels of the mucosa, and not directly into the lumen of the bowel. These eggs may be in the "tadpole" stage of development, but more commonly they contain rhabditiform larvae nearly ready to hatch. Rarely they hatch in utero. Hatching ordinarily takes place soon after the eggs are deposited in the tissues, but some eggs may be discharged into the lumen of the bowel before hatching occurs. The larvae in the tissues may soon work their way out of the wall into the lumen of the bowel or may remain for weeks as active forms, feeding on the cells of the mucosa. Whether in the mucosal layer or in the lumen of the upper small intestine, they grow in size but have never been found to metamorphose into filariform larvae at this level. Farther down the intestine, particularly in the colon and rectum, as well as in the expelled feces, they become appreciably smaller than they were in the duodenum or jejunum. Some of the larvae, which remain in the tissues for weeks, become encased in delicate hyaline capsules; this tends to prolong their stay in the intestinal wall.

It is evident, therefore, that the several conditioning factors which govern the discharge of larvae from the tissues into the lumen of the bowel, the rapidity of movement of the contents down the bowel and

the death and disintegration of the larvae in the lower part of the bowel make it impossible to judge the egg-laying capacity of the females by the daily discharges of larvae in the feces. Careful counts of measured samples of feces over a period of weeks furnish approximate information of productivity, particularly when such counts are conducted at various intervals during the egg-laying period. Because of the difference in egg production at different times during this period, the larvae discharged in the stool furnish no criterion of the number of female worms actually present in the upper part of the intestinal wall. These observations stand in marked contrast to those for hookworms, Ascaris and Trichocephalus, for which a relatively accurate estimate of the number of female worms present in the bowel may be made by egg counts of measured samples of feces. However, in the case of Strongyloides, egg or larval counts of measured samples of feces over a period of several days furnish an approximate idea of the egg-laying capacity of the mother worms at the particular period in the productive cycle.

In view of these observations on egg production in dogs infected with human strains of S. stercoralis and in a rhesus monkey infected with a chimpanzee strain of Strongyloides morphologically and physiologically resembling human strains of S. stercoralis, the question arises as to what conditions are responsible for reduction in fecundity. First of all, as we have indicated previously, the period of egg production of S. stercoralis in the dog is relatively short compared with that in the human host. We regard this mechanism in the two hosts as qualitatively similar but differing as to time elements. A month's period in the dog may be comparable to a year's duration of the same strain in man, while in the monkey the productive period apparently lies between these extremes. We have demonstrated that the period of fecundity of parasitic females in homologous human strains varies within wide limits in different dogs. Hence two separate factors apparently operate in determining the actual process, namely (1) the compatibility of the host species and (2) the relationship of the individual host to the parasite. So far as we have been able to study cases of Strongyloides infection in man and autochthonous infections in monkeys, we have found that they also exhibit this same individual relationship.

It is possible that at the time of the migration of preadolescent and adolescent female Strongyloides from the lungs to the intestinal tract some of the worms pass down the bowel and out in the feces before they have matured or have had an opportunity to enter the intestinal wall, just as the majority of the parasitic males do. After maturity and penetration of the intestinal mucosa the possibility of such a miscarriage is more remote. As a matter of fact, in many thousands of fecal films of dogs infected with Strongyloides which we have examined daily

(5 Gm. samples of feces), during the prepatent, productive and postproductive periods, with a single exception (dog 60), we have never found the slightest evidence of female worms being discharged in the stools. If such a spontaneous discharge of living females from the intestinal mucosa did occur in any appreciable numbers, it might be expected that worms evacuated from higher levels would have an opportunity to reenter the mucosa at lower levels, so that, in the older infections, the larger numbers of worms would be found in successively more distal regions of the intestinal wall. An examination of our data fails to furnish supporting evidence for this assumption. In moderate infections (from 100 to 250 female worms), irrespective of the duration of the infection (dog 62, fourteen days; dog 64, forty-two days; dog 58, eighty-nine days; dog 50, one hundred and twenty days, and dog 48, one hundred and forty days), there was in each case a fairly equal distribution through the duodenum and jejunum, with few worms in the wall of the ileum. In heavier infections (from 400 to 850 female worms) there was a greater tendency than in light infections for a larger number of worms to accumulate in the wall of the posterior jejunum and ileum, although this was likewise not correlated with the duration of the infection (dog 63, forty-one days; dog 60, forty-one days; dog 59, forty-nine days; dog 61, eighty-five days, and dog 41, five months). There were, however, no indications of an actual loss of females in the duodenum being compensated by involvement of the lower levels of the bowel. Thus the reduction in total egg production in any particular infection cannot reasonably be assigned to the evacuation of females from the mucosa. On the contrary, our evidence points to a retention of females within the wall of the dog's intestine for at least several months after the production of eggs has been reduced to zero. A loss of fecundity rather than a loss of female worms, therefore, appears to be the determining factor. What, then, brings parturition to an end?

In our examination of "old" parasitic Strongyloides females which are near the end of their productive period we have commonly found 1 or 2 eggs in each horn of the uterus (fig. 2). Such eggs are invariably in the one cell stage and may appear to be well formed, but never proceed with cleavage in utero or after being teased out of the worm. As far as we have been able to test these eggs, they are nonviable. In other females of the same type the few uterine eggs seen are poorly formed, and their contents unorganized. In both of these types there is little, if any, evidence in the ovaries of egg-forming material. In "older" (i. e. postproductive) females, eggs of any description have ceased to be formed; the ovaries are atrophied, and the oviducts and uteri have collapsed. The appearance of all these worms in the tissues

suggests contraction, but when they are removed to physiologic solution of sodium chloride at either 22 or 37 C., they readily elongate and become active. Their digestive tracts are still complete and functional. Except for their sexual functions they appear to be normal. Usually these worms, as they "age," become surrounded by an epithelial cellular capsule, which, in turn, may be encased in a layer of polymorphonuclear leukocytes, or less commonly of eosinophils and monocytes. We have never seen a productive female so encapsulated. It appears, therefore, that reduction in egg production and, finally, complete cessation of this activity are probably due to a local reaction in the tissue of the host.

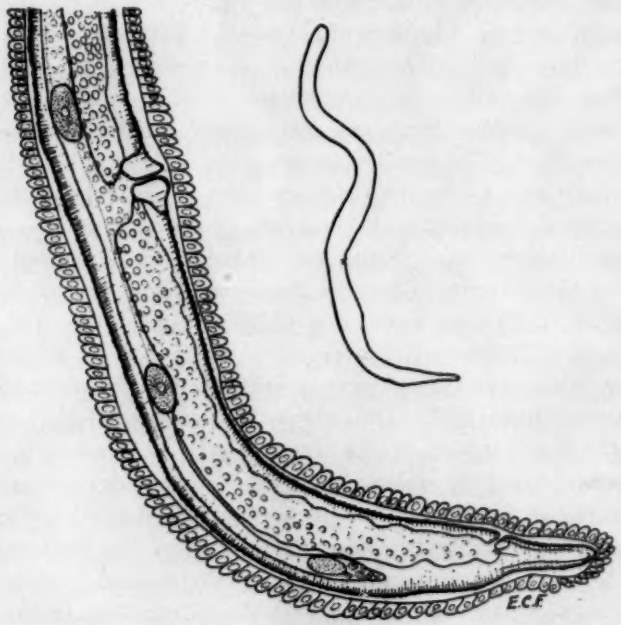


Fig. 2.—Parasitic female Strongyloides from the upper duodenum of dog 58 at autopsy on the eighty-ninth day after inoculation. The worm is near the end of the egg-producing period. To the right there is an outline of an entire worm, completely dissected out of the tissues, × 80; to the left, the posterior portion of the worm in its adventitious epithelial capsule is shown. Two apparently fertile eggs may be seen, one in each horn of the uterus. A small amount of egg-forming material is present in the distal end of the posterior ovary. Drawings by means of camera lucida; × 280.

This argument is strengthened by additional observations on these "old" females. In some cases the encapsulated worms take on a transparent glossy appearance which makes it difficult to recognize them in films of freshly scraped tissue. Such worms appear to be slowly dying and, on dissection from their adventitious capsules, move sluggishly.

They disintegrate readily under light pressure. Again, worms have been seen from time to time in which the capsule has been partially broken down, with the result that phagocytic cells in the tissue of the host have attacked and partially destroyed one end of the parasite, while the rest of the worm remained alive (fig. 3). These observations suggest the eventual destruction of the complete worm in situ. While this type of local reaction of the tissue as a protective mechanism for the host is not unique, it is far less rapid in strongyloidosis than in trichinosis or cysticercosis (cellulosae). This milder, slower reaction is probably associated with the lower toxicity of the female Strongyloides.

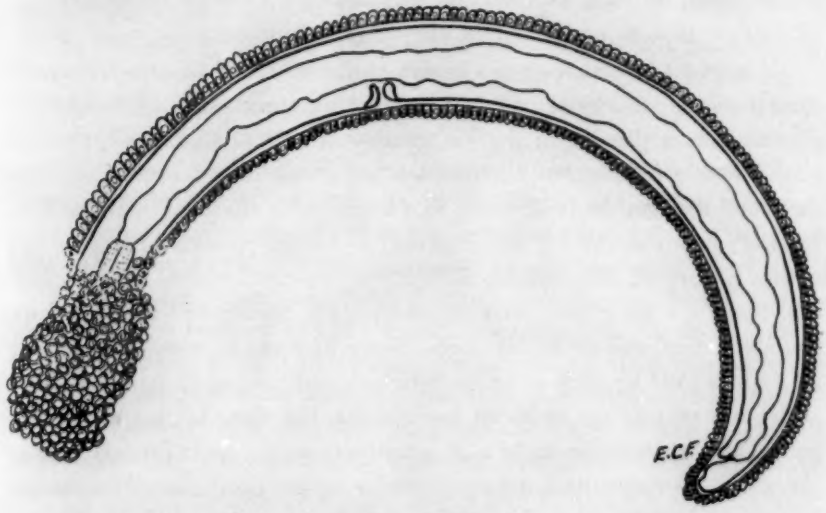


Fig. 3.—Postproductive female Strongyloides, within epithelial capsule. All the sexual organs except the vulvar sphincter have degenerated. A group of macrophages has broken down the capsule at the anterior end of the worm and phagocytosed almost the entire esophageal third of the worm. This is the only worm recovered from dog 8 (not in this series), six and a half months after inoculation. The last larvae in the feces were seen three months previously. Drawing by means of camera lucida; × 200.

The presence of postproductive parasitic females in the intestinal wall of the host materially complicates the question of specific diagnosis and the correct analysis of the clinical picture. Within the past five years one of us (E. C. F.) has seen twenty-five human cases which did not show a Strongyloides infection in examination of three fecal films but in which a single rhabditiform larva was recovered after complete examination of 5 gm. of feces which had been carefully concentrated. In three additional cases clinical and hematologic studies suggested strongyloidosis, although larvae were never recovered in stool concen-

trates. If our canine studies may be used as a criterion, we may expect that either or both of these human types may harbor from several dozen to several hundred postproductive parasitic females, the toxins from which are gradually being absorbed into the system, producing the vague toxic symptoms so characteristic of infection with Strongyloides—frequently a leukopenia and a mild eosinophilia, with or without erythropenia. We are convinced that in many cases in which no organisms have been found a careful prolonged search of at least one 5 Gm. specimen of freshly passed feces will result in the discovery of a few larvae of Strongyloides. It is equally important to remember that the number of larvae found by fecal examination may not be a criterion of the number of female worms embedded in the intestinal mucosa.

If internal infection occurs in the course of a few months in experimental canine strongyloidosis of human origin, increasing the number of female worms present in the intestinal wall and producing a group of young fertile females, it is altogether likely that over a period of years the same mechanism is at work in man, who is the most suitable host for the human strains of the organism. Among persons of middle age with a history of strongyloidosis of from fifteen to twenty years' standing, there are some who have apparently not been reinfected from the soil since childhood or adolescence. Some of these persons are seriously ill, as indicated by their neurotic behavior and profound malaise. Their blood may or may not show an eosinophilia, but there is usually a leukopenia. They have the signs of a slowly operating toxic process. They are usually constipated but have digestive upsets on the slightest dietary indiscretions, following which there is marked diarrhea, with the passing of mucus in the unformed feces. Examination of the stool may reveal a few rhabditiform larvae of Strongyloides; rarely will any considerable number be found. In view of our observations on canine strongyloidosis we are inclined to doubt that in man the female parasite can remain fertile for as long as from fifteen to twenty years. We, therefore, suggest that in such cases the parasites may have been maintained by internal reinfection, even though at the time of examination there is no evidence of dwarf filariform larvae in the feces. Certainly such an explanation has much in its favor and clarifies many of the difficulties which have surrounded these difficult cases of long continued human strongyloidosis. However, one must not overlook the pulmonary focus of adult parasitic female Strongyloides as a secondary location from which reinfection may be initiated.

CONCLUSIONS

Series of controlled experiments on dogs and on a rhesus monkey, undertaken to study the differences in fecundity of parasitic female Strongyloides, and, if possible, to determine the cause of these differences, have indicated that the experimental host may be inoculated with equal success when the filariform larvae in the infective stage are introduced (1) cutaneously on the abdominal wall, (2) orally or (3) intracecally.

After the prepatent period the number of eggs produced by the female worms rises rapidly to a peak, declines to a lower level which is maintained for a period of time and then descends lower and lower, finally reaching a base level of zero.

At the beginning of the egg-laying period, or shortly thereafter, the parasitic females invade the intestinal mucosa, usually in the region of the duodenum or jejunum, where they deposit their eggs, ordinarily quite well developed, into the tissues. The eggs usually hatch, and the rhabditiform larvae gradually work their way out into the lumen of the bowel, pass down and are evacuated in the stools. (In simian infections eggs are more commonly passed in the feces and hatch later.) In canine infections some larvae become encapsulated in the mucosa.

Random fecal samplings and culture methods are unsatisfactory indexes of the number of eggs or larvae expelled in the feces. Daily counts of 5 Gm. samples of feces, from which total daily discharges of larvae may be calculated, have been found to be a more reliable measure of such discharges. Great care must be exercised in identifying the larvae, since as many as 90 per cent may be dead or disintegrating at the time of evacuation. Even with these precautions there is a marked daily fluctuation in the counts; this does not appear to be correlated with the actual egg production of the female worms. The average of counts over a period of a week or more, therefore, provides an approximate estimate of the level of production rather than an accurate gage of the productivity of the females.

Daily counts and averages of weekly counts of larvae (or eggs) in the feces are usually far in excess of the number of uterine eggs in the parasitic females, indicating that, on the average, the worms produce from two to four times as many eggs as can be accommodated in their uteri at any one time.

The yield of parasitic females at autopsy is frequently in excess of expectations based on the number of filariform larvae in the inocula. In two experimental animals these mother worms actually exceeded the number of larvae in the infective mediums to which these animals were exposed. This excess can be explained only by the mechanism of internal infection (hyperinfection), by which daughter rhabditiform

larvae transform into dwarf filariform larvae as they pass down the bowel, enter the blood stream through the mucosa of the large bowel, and effect a migration through the lungs and thence to the upper intestinal tract via the respiratory passages, glottis, esophagus and stomach.

Many of the female worms recovered at autopsy were at or near the end of their period of fecundity. In several of these infections larvae had not been recovered from the feces for several weeks or months preceding the death of the host. Such worms were still alive and became active on removal to physiologic solution of sodium chloride, but showed concrete evidence of the termination of the egg-laying period. Many of these worms in the intestinal wall were encapsulated and some were surrounded by layers of white cells, primarily polymorphonuclear leukocytes. In a few instances the capsules had been broken, and the worms were in the process of being phagocytosed.

The reduction in egg production and the eventual loss of adult female worms by the host is not due to the migration of the organisms out of the intestinal mucosa and to their being discharged in the feces, but to encapsulation and phagocytosis by the cells in the tissue of the host, a process comparable in type but not in rapidity to the reaction of the cells to Trichinella larvae or to Cysticercus cellulosae. It is suggested that this difference is due to the lower toxicity of Strongyloides.

Infection of dogs with human strains of Strongyloides is maintained for only a period of weeks or months, as contrasted with a period of years in man, the natural host. The period of infection in the monkey lies between these two extremes. Nevertheless, unless internal infection is predicated, it is inconceivable that man remains infected for a period of from fifteen to twenty years without outside exposure or hyperinfection.

In considering the applications of this study to human strongyloidosis, it may be concluded that: (1) there is a need for prolonged intensive fecal examination in suspected cases before the patient is pronounced free from organisms; (2) even when no evidence of organisms is found, such patients may harbor in the intestinal wall several tens or hundreds of postproductive females which may be responsible for characteristic toxic symptoms of chronic strongyloidosis; (3) the number of larvae present in the stools of patients with strongyloidosis is not necessarily an index of the severity of their infection, and (4) internal infection (hyperinfection) is the only satisfactory explanation for prolonged chronic strongyloidosis.

SUMMARY

On the basis of an intensive experimental study of human Strongyloides in young dogs and of a chimpanzee strain of the organism in a rhesus monkey, concrete evidence has been obtained, indicating that following the period of incubation the parasitic female worms produce

eggs, the number of which rapidly increases and then gradually decreases to zero. This phenomenon is due not to the escape of the worms from the mucosa of the upper levels of the small bowel, but to reactions in the tissues of the host, including first encapsulation of the egg-laying females and later cellular infiltration around, and phagocytosis of, the worms. Ordinary fecal examination for larvae of Strongyloides has been found a very unsatisfactory criterion of the presence or numbers of parasitic females, in view of the frequent disintegration of larvae en transit down the bowel and because of the gradual reduction in the egg production of the mother worms. Although fecal examinations may consistently fail to disclose the organism for a period of weeks or months, a considerable number of female worms may still be present in the duodenal and jejunal mucosa and be responsible for chronic toxic manifestations. Internal infection (hyperinfection) is offered as an explanation for prolonged human strongyloidosis.

NECROSIS OF THE MYOCARDIUM INDUCED BY THE ORTHOPHOSPHATES

F. A. McJUNKIN, M.D.

W. R. TWEEDY, PH.D.

AND

W. J. MENCKY, B.S.

CHICAGO

In an earlier publication [1] it was shown that destructive lesions produced by injections of parathyroid hormone are toxic and not secondary to circulatory disturbances. The ultimate mechanism of the toxic action of the hormone was not explained, but because of the characteristic effect of the hormone on the calcium and phosphorus metabolism it was thought that a serious disturbance in one or the other might be the indirect, if not the direct, cause of the necrosis observed. The purpose of the experiments reported here was to study the effects of injected orthophosphates under conditions that prevented their rapid elimination and hence favored their accumulation in the blood.

Whole human blood was found by Kay and Byrom [2] to contain an average of 38.4 mg. of phosphorus per hundred cubic centimeters. Of this amount, 2.9 mg. was in the form of inorganic phosphate. In health the fluctuations from these values were not large. Addis, Meyers and Bayer [3] reported that the concentration of inorganic phosphate in the blood plasma was about proportional to the rate of urinary excretion, and that the kidneys quickly responded to changes in the ingestion of phosphorus phosphate. These authors caused both the concentration of the plasma and the urinary output to rise by injecting a neutral solution of sodium phosphate (75 mg. of phosphorus per kilogram of body weight). Within from two to three hours after the injection the concentration of the plasma had fallen to near normal, as the phosphorus was excreted by the kidneys. Binger [4] injected into dogs amounts of orthophosphates equivalent to 150 mg. per kilogram of body weight. The serum calcium dropped from its normal level of 10 mg. per hundred cubic centimeters to approximately 6 mg. Binger stated that at that

From the Departments of Pathology and Biochemistry, Loyola University School of Medicine.

1. McJunkin, F. A.; Tweedy, W. R., and Brenhaus, C.: Arch. Path. **14**: 649, 1932.

2. Kay, H. D., and Byrom, F. B.: Brit. J. Exper. Path. **8**:240, 1927.

3. Addis, T.; Meyers, B. A., and Bayer, L.: Am. J. Physiol. **72**:125, 1925.

4. Binger, C. A. L.: J. Pharmacol. & Exper. Therap. **10**:105, 1917.

level a condition of tetany supervened, provided that the neutral or alkaline salts had been injected. With acid phosphate solutions the drop in calcium occurred unaccompanied by tetany.

In our experiments we stopped the rapid outflow of injected phosphates by performing bilateral nephrectomy. Special attention was given the cardiac muscle to determine the histologic effects of the injections of orthophosphates, and chemical estimations of the phosphate phosphorus in the blood were made in order to determine whether the incidence of necrosis could be attributed to increased amounts of phosphates in the blood.

METHODS

Histologic Methods.—Kidneys of young albino rats were removed after ligation of the ureters and vessels at the hilus. The abdominal wounds were closely sutured and sealed with collodion and gauze. All the animals were killed when the experiments were terminated, and the tissues were immediately placed in formaldehyde for fixation. Our procedure was to examine the tissues for necrosis and not for lesser degenerative changes. For this purpose paraffin sections were made and stained with hematoxylin and eosin.

Chemical Methods.—The inorganic and total phosphorus of the whole blood were determined by the method of Fiske and Subbarow[5] as modified by Hauch and Koch[6] for small quantities of blood. Blood serum calcium was determined by the Kramer and Tisdall method[7] as modified by Tweedy and Koch.[8] Dried heart muscle was wet ashed with sulphuric acid and hydrogen dioxide and analyzed for total phosphorus by the methods already described.

EFFECTS OF BILATERAL NEPHRECTOMY ON INORGANIC PHOSPHORUS OF THE BLOOD AND MUSCLE OF THE HEART

During the first hour following nephrectomy the inorganic phosphorus of the whole blood had risen slightly to 6.5 mg. per hundred cubic centimeters, as compared with an average value of 5.1 mg. in seven normal rats (footnote, table 2). After six hours a definite increase in inorganic phosphorus had appeared (rat 2, table 1). Within eight hours it had increased further to 13.1 mg. and at the end of twelve hours to 13.9 mg. At the end of twenty-four hours there was an average value of 17.7 mg., and after forty-eight the average value was 21.7 mg.

The hearts of the animals were examined histologically for necrosis, but none was observed, except in rats killed forty-eight hours after nephrectomy. In one of these (rat 12) necrosis was distinct. Less severe degenerative changes were not determined by the technic used.

5. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.

6. Hauch, J., and Koch, F. C.: Unpublished data, personal communication to the authors.

7. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475, 1921.

8. Tweedy, W. R., and Koch, F. C.: J. Lab. & Clin. Med. **14**:747, 1929.

EFFECTS OF BILATERAL NEPHRECTOMY AND INJECTIONS OF DISODIUM HYDROGEN PHOSPHATE

It at once became clear that the reaction of the nephrectomized rat to the injection of phosphate was unlike that of the normal animal. Small doses of phosphate, which were nontoxic for normal rats, pro-

TABLE 1.—*Effects of Bilateral Nephrectomy* *

Rat	Weight, Gm., Individual or Average	Hours After Nephrectomy	Blood Inorganic Phosphorus, Mg. per 100 Cc., Individual or Average	Necrosis of Myocardium
1	124	1	6.5	0
2	106	6	7.8	0
3	120	8	13.1	0
4–5	90	12	13.9	0
6–9	186	24	17.7	0
10–12	133	48	21.7	+ or doubtful

* In all the tables + indicates single necrotic fibers, ++ intermediate degrees of necrosis and +++ necrotic areas.

TABLE 2.—*Effects of Bilateral Nephrectomy and Intraperitoneal Injections of Solution of Disodium Hydrogen Phosphate*

Rat	Weight, Gm., Individual or Average	Hours After Nephrectomy	Phosphorus Injected,* Individual or Average	Blood Inorganic Phosphorus, Mg. per 100 Cc., Individual or Average	Necrosis of Myocardium
1–3	117	48	2.6	19.8	++
4–6	248	48	4.4	20.6	Doubtful
7–10	178	24	3.4	21.4	Doubtful
11–12	119	7	2.7	11.0	0
13–14	130	3	2.9	6.7	0
15	120	1½	2.8	8.3	
16	133	¾	3.6	5.9	
17–19	144	24	6.8	...	++
22–22	112	24	12.8	30.9	+++
23–25	116	24	3.2	12.8†	
26–31	114	24	3.2	14.2†	
32–37	121	4¼	32.3	53.3	

* Injections were made intraperitoneally immediately following closure of the abdominal incision. A solution of disodium phosphate, which contained 0.75 Gm. of the salt per hundred cubic centimeters, was diluted appropriately before injection.

† The average total blood phosphorus for rats 23 to 25 was 85.2 mg. A total blood phosphorus of 51.3 mg. was the average in seven normal rats of an average weight of 132 Gm., and in the same normal animals the inorganic phosphorus had an average of 5.1 mg. In six additional nephrectomized rats which received injections (rats 26 to 31) the average total blood phosphorus was 88.4 mg.

duced destructive lesions in the nephrectomized animals, and larger doses, while nontoxic for normal rats, were lethal for the nephrectomized rat. Rats 1 to 3, although given injections of small doses of the basic disodium hydrogen phosphate, showed much myocardial necrosis. In the larger animals the amount of necrosis was small or absent, and later in the work it was found that rats which weighed about 100 Gm. were most susceptible to the cardiac injury. Rats which weighed more than 100 Gm. were resistant and showed the necrosis irregularly. In

severe lesions, such as that seen in rat 1 (table 2), the necrotic areas were of sufficient size to be seen on gross examination as opaque foci in the ventricular walls.

The lesions were in proximity to the coronary vessels. Necrosis also appeared in the media of the first part of the aorta and was occasionally seen in the walls of the larger coronary arteries. The earlier of the lesions appeared microscopically as myomalacia, while at the end of forty-eight hours many leukocytes had accumulated about the necrosis, which made the focus much more distinct.

Deposition of calcium in both the cardiac and the aortic lesions was observed. In the striated musculature of the abdominal wall necrosis was seen, but the lesions of the myocardium were the most severe. Repeated examination of the liver, lungs and suprarenal glands failed to show destructive lesions. In the wall of the stomach beneath the muscularis mucosae there was often much edema.

It is clearly seen in table 2 that the necrosis resulted from the combined effect of the nephrectomy and the injected phosphate and that doses of from 6.8 to 12.8 mg. (rats 17 to 22) regularly produced the myocardial injury.

The many determinations of blood inorganic phosphorus and total phosphorus which were made from twelve to twenty-four hours after nephrectomy and the injection of small doses of phosphate showed only a doubtful relationship of either of these values to the incidence of myocardial necrosis. On the other hand, nephrectomized rats which received injections of doses sufficiently large to produce regularly the myocardial lesions showed an average inorganic phosphorus of 30.6 mg. at the end of twenty-four hours (rats 20 to 22, table 2), as compared with a value of 17.7 mg. in nephrectomized rats not given injections (rats 6 to 9, table 1). The movement of larger doses of phosphates injected intraperitoneally into the blood stream was shown in a striking fashion, since by this experiment the blood inorganic phosphorus was increased in six rats (32 to 37, table 2) to an average of 53.3 mg. within an average time of four and a quarter hours. Normal rats given injections of comparable doses showed no ill effects, and the blood inorganic phosphorus in three normal rats was elevated to an average of only 9.4 mg. After large injections into normal rats no lesions were seen in the heart on histologic examination.

EFFECTS OF BILATERAL NEPHRECTOMY AND INJECTIONS OF OTHER ORTHOPHOSPHATES

It was thought that the moderate tendency of the basic disodium hydrogen phosphate to produce alkalinization might influence the reactions resulting from the administration of the salt. In rats 1 to 3

(table 3), weighing from 176 to 200 Gm., which received small doses of a solution of disodium and monopotassium phosphates buffered to p_H 7.1, the inorganic phosphorus of the blood was approximately the same as in rats receiving the basic disodium hydrogen phosphate alone, and there was no necrosis of the myocardium. When the buffered solution was injected into smaller rats (4 to 7) a slight amount of necrosis was seen.

Since it has been determined that tetany in the dog is not produced by injections of the monosodium phosphate, the effect of this salt on the cardiac muscle was investigated. In rats 8 to 14 (table 3) it appears that this acid phosphate did not affect the heart so much as the disodium salt, and large doses (rats 15 to 17) caused less severe lesions than comparable doses of disodium hydrogen phosphate. Rats given injec-

TABLE 3.—*Effects of Bilateral Nephrectomy and Injections of Monosodium Phosphate, Disodium Phosphate, Trisodium Phosphate and Di-Ammonium Phosphate*

Rat	Weight, Gm.	Hours After Nephrectomy	Phosphorus Injected, Mg.	Type of Solution Injected	Blood Inorganic Phosphorus, Mg. per 100 Cc.	Necrosis of Myocardium
1-3	188	24	6.7	Buffer 1*	21.6	0
4-7	131	24	5.5	Buffer 2*	15.3	+
8-10	159	24	4.3	Monosodium phosphate	15.2	0
11-14	123	48	4.8	Monosodium phosphate	....	0
15-17	125	24	11.3	Monosodium phosphate	25.5	++
18-19	129	24	20.0	Sodium carbonate	....	0
20-21	99	24	50.0	Sodium chloride	....	0
22-26	88	27	9.6	Di-ammonium phosphate	36.1	0

* Buffers 1 and 2 were mixtures of disodium hydrogen phosphate and potassium dihydrogen phosphate buffered to p_H 7.1 and 7.2, respectively. Rats 5 and 6 also received a subcutaneous injection of 2 cc. of a 0.5 per cent solution of sodium carbonate. Rats 18 and 19 received sodium carbonate alone. Rats 20 and 21 were given injections of sodium chloride alone.

tions of varying doses of di-ammonium phosphate (rats 22 to 26) showed no destructive myocardial lesion. The small doses of trisodium phosphate which were injected produced no change in the heart. A buffered solution of phosphate when combined with sodium carbonate injected subcutaneously (rats 5 and 6, table 3) revealed no increase of myocardial damage. Indications that the sodium ion was not responsible for the myocardial necrosis were obtained by injections of sodium chloride (rats 20 and 21). Sodium carbonate was also without effect (rats 18 and 19).

RELATIONSHIP OF MYOCARDIAL NECROSIS TO SERUM CALCIUM AND INJECTIONS OF CALCIUM GLUCONATE

Up to this point it appeared that the lesion in the heart was caused directly or indirectly by the phosphate ion of the injected phosphate and that its production was favored by the use of the basic salt. We

were impressed by the tendency of the lesions to calcify and were led to investigate the calcium content of the serum and the effect of injections of calcium gluconate.

In view of the well known evidence indicating the mutual control of the concentration of calcium and phosphate ions in the blood plasma, it was thought that a rapid rise in the blood inorganic phosphate induced by nephrectomy or nephrectomy plus injected phosphates might be reflected in a value for serum calcium well below normal. The serum calcium was determined in two nephrectomized rats (8 and 9, table 4) which had been given injections of about 5 mg. of phosphate phosphorus. About twenty-four hours later, the serum calcium was 10.8 and 11.4 mg. per hundred cubic centimeters, respectively, while the phosphorus had risen to 17.8 and 16.0 mg., respectively. Then

TABLE 4.—*Serum Calcium After Bilateral Nephrectomy and Injections of Disodium Phosphate*

Rat	Average Weight, Gm.	Hours After Nephrectomy	Phosphorus Injected, Mg. per 100 Cc., Individual or Average	Serum Calcium, Mg. per 100 Cc., Individual or Average	Blood Inorganic Phosphorus, Mg. per 100 Cc., Individual or Average
1-3	162	24	0	8.95	
4-5	213	3½	58.2	8.08	
6-7	147	1¼	40.1	8.22	
8-9	208	21	4.7	11.10	16.9
10	220	72	2.8	11.80	20.3
11-12	178	24	19.2	6.73	
13-14	190	4	21.1	9.24	
15-16	158	2	16.6	8.63	
17-18	202	16	21.0	8.53	
19-20	190	6	20.0	9.28	
21-22	204	12	22.3	6.73	
23-25	214	9	22.8	7.85	

rats 11 to 25 were given injections of an amount of phosphorus that produced regularly myocardial necrosis. At the end of from eight to twelve hours a slightly lowered calcium level was observed, and after twenty-four hours there was pronounced hypocalcemia. Large doses of phosphate (rats 4 to 7, table 4) lowered the calcium level only moderately within from one and a quarter to three and a half hours. At the end of twelve hours, however, a dose of 22.3 mg. caused marked hypocalcemia (rats 21 and 22).

These results show that even in nephrectomized rats it is necessary to use an amount of orthophosphate greatly in excess of the toxic dose in order to demonstrate a sudden lowering of the serum calcium. Several experiments made in connection with another investigation demonstrated that the serum inorganic phosphorus may reach a value of three or four times its normal concentration as a result of nephrectomy, while the serum total calcium may either remain within its normal range or fall to not more than 10 per cent below the average total

serum calcium of normal rats. As the chemical methods used in this investigation measured total amounts of serum inorganic phosphorus and calcium and since no reliable methods for the measurement of the concentration of the calcium and phosphate ions were applicable, it is by no means certain that the relationship of these ions was undisturbed.

Collip [9] stated that lesions could not be produced by injections of calcium salts alone. However, by the injection of huge amounts (400 mg.) of calcium gluconate into normal small rats weighing less than 150 Gm. we [1] were able to produce small foci of necrosis in the kidneys. In the nephrectomized rat an intraperitoneal dose of about 75 mg. of the gluconate was sufficient to cause severe destructive lesions in the myocardium and the aortic media (table 5). In both locations the necrotic areas showed within forty-eight hours the same tendency to calcify observed in the "phosphate" lesions.

TABLE 5.—*Effect of Bilateral Nephrectomy and Injections of Calcium Gluconate*

Rat	Average Weight, Gm.	Hours After Nephrectomy	Calcium Gluconate Injected, Mg. per 100 Cc.	Serum Calcium, Mg. per 100 Cc.	Blood Inorganic Phosphorus, Mg. per 100 Cc.	Myocardial Necrosis
1	284	24	75	9.51	....	++
2	278	24	75	10.36	37.5	+
3	238	24	60	9.62	20.8	+
4	282	24	85	19.40	19.0	
5	335	24	95	15.14	12.6	
6	235	24	65	10.00	16.0	+++
7	300	24	80	10.40	21.8	+++
8	310	72	110	.....	....	++*

* There was also much calcification in the media of the coronary artery, as shown by staining with both hematoxylin and eosin.

In only two instances (rats 4 and 5, table 5) was there pronounced hypercalcemia. On the other hand, the inorganic phosphorus reached an average concentration well above that found in nephrectomized rats which did not receive injections. Inability of the excess calcium to hold back the mounting phosphorus level permitted this condition of both hyperphosphatemia and hypercalcemia to develop in the blood at the end of the twenty-four hour period.

COMMENT AND SUMMARY

It is recognized that with the cessation of renal function there ensues a variety of progressive chemical changes in the organism. In discussing the effects of ligation of the ureters in the dog, Atchley and Benedict [10] stated:

> Profound changes occur in the distribution of the electrolytes of the blood and tissues. The net effect on the blood serum is, in résumé, a retention of

9. Collip, J. B.: Am. J. Physiol. **76**:742, 1926.

10. Atchley, D. W., and Benedict, E. M.: J. Biol. Chem. **73**:1, 1927.

phosphate and sulphate which takes base from carbonate and chloride. This equimolecular interchange occurs regardless of the movement of water to or from the tissues, and seems to have no effect on the total base content.

It is evident that as a result of these changes an ultimate condition of acidosis supervenes. The data presented here show that it is approximately forty-eight hours after nephrectomy, when the aforementioned changes are probably well advanced, that histologic evidence of beginning necrosis may appear in some animals. However, injection of orthophosphates into the rat immediately after nephrectomy in quantities that do not kill or produce histologic lesions in the normal rat injured the cardiac muscle to such an extent that necrosis appeared regularly at the end of twenty-four hours in the animals studied. In connection with our experimental data, it has been pointed out that the lesions are produced in the nephrectomized animal with either alkalosis or some degree of acidosis such as may be produced by the dihydrogen phosphate. That alkalosis rather than acidosis favors the production of the lesion is probably indicated by the failure of di-ammonium phosphate to produce myocardial necrosis. In the varied chemical analyses made we obtained no direct evidence that the injected orthophosphates actually entered the cells of the myocardium and initiated the changes responsible for the necrosis observed. Determinations made on the desiccated hearts of nephrectomized rats which were given injections showed no greater total phosphorus than in the cardiac muscle of normal rats. Application of the Fiske-Subbarow-Mallory method [11] to pyroxylin (celloidin) sections prepared from the hearts with the "phosphate" lesions showed no microscopic evidence of excess phosphorus.

Early calcification of the "phosphate" lesions was frequently seen. Our experimental data reveal hyperphosphatemia at the time that the myocardial necrosis was developing. With an excess of phosphate ions in the part, there would be a tendency toward precipitation of calcium entering the area or already in it. The similarity of the "phosphate" lesions and lesions caused by injections of calcium gluconate leads one to suspect a similarity in their pathogenesis. Ham and Lewis,[12] in a study of lesions caused by viosterol, regarded the deposition of calcium as the primary causative factor in their production. In our investigation [1] of lesions caused by parathyroid hormone it was made clear that in no instance was calcification observed, except in association with destructive tissue changes. Since calcification in the microscopic sense represents a great absolute increase of calcium in the tissues affected, it may well be that excess calcium was thrown out of solution for a considerable time before its histologic appearance. Other types of injury

11. Mallory, F. B.: Am. J. Path. **9**:557, 1933.

12. Ham, A. W., and Lewis, M. D.: Arch. Path. **17**:356, 1934.

to the myocardium of the rat apparently manifest little affinity for calcium salts. The heart was "snagged" by means of syringe needles and examined at twenty-four, forty-eight and seventy-two hour intervals. Although conspicuous necrotic foci were present along the needle tract, no trace of calcification was present.

CONCLUSIONS

Myocardial necrosis may be produced by the injection of disodium phosphate into small nephrectomized rats. Lesions closely resembling the "phosphate" necrosis may be produced by the injection of calcium gluconate into nephrectomized rats. Both kinds of lesions show a tendency to early calcification. The chemical and histologic evidence indicates a close relationship between the necrosis and the deposition of calcium. In view of the tendency of the myocardial necrosis to become calcified it may be assumed that the precipitation of calcium and phosphate ions represents a local condition of tissue in which the highly organized parenchymal cells of the myocardium cannot survive.

CONCURRENT TUMORS OF THE LEFT CAROTID BODY AND BOTH ZUCKERKANDL BODIES

RICHARD W. CRAGG, M.D.
Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN.

The carotid body was first described by von Haller,[1] in 1743, and again by Neuber,[2] in 1783. However, little attention was paid to their work, and it remained for the detailed description of Luschka,[1] in 1862, to stimulate genuine interest. Marchand,[3] in 1891, was the first to describe a tumor of the carotid body, and Paltauf,[3] in 1892, was the second. Since that time a great number of reports of tumors of these bodies have appeared in the literature. The reports have been extensively reviewed in the past six years by Talman,[1] Bevan and McCarthy [4] and Rankin and Wellbrock.[5] The investigators last mentioned recorded one hundred and ninety-six cases. Thus, it is apparent that tumors of these glands are not rare, even though they may have been reported infrequently.

In 1901, Zuckerkandl [6] discovered and described in detail, two small bodies which lie on the anterior surface of the abdominal aorta, one on each side of the point of origin of the inferior mesenteric artery. He found that these small bodies were consistently present and easily visible in all human fetuses from 5 months of age to full term, but that after this period they atrophied rapidly, so that at 2 years of age they were difficult to find and by the tenth year they could be found only by serial sectioning of the tissue in the regions in which they were known to occur in early life. He further noted that the bodies possessed the same histologic appearance as that of the carotid body and suprarenal medulla. The minute periaortic masses have since been known as Zuckerkandl bodies or glands.

This work was done under the direction of Dr. John deJ. Pemberton, Division of Surgery, the Mayo Clinic.

1. Quoted by Rankin and Wellbrock.[5]
2. Neuber, quoted by Bevan and McCarthy.[4]
3. Quoted by Rabin.[22]
4. Bevan, A. D., and McCarthy, E. R.: Surg., Gynec. & Obst. **49**:764, 1929.
5. Rankin, F. W., and Wellbrock, W. L. A.: Ann. Surg. **93**:801, 1931.
6. Zuckerkandl, E.: (*a*) Verhandl. d. deutsch. anat. Gesellsch. **15**:95, 1901. (*b*) The Development of the Chromaffin Organs and of the Suprarenal Glands, in Kiebel, Franz, and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 157.

In 1865, Henle discovered that in the suprarenal gland, fixed in a solution containing a chromium salt or acid, a yellowish-brown pigmentation, which he described as granular, developed frequently in the medullary cells. This fact was confirmed by Soulié,[7] Kohn,[8] Wiesel[7] and many others, and was called the chromaffin reaction, because of the affinity of the medullary tissue for the chromium salts. Stilling,[9] in 1892, was the first to demonstrate the presence of this reaction in cells of the carotid body; this was confirmed by Kohn and Zuckerkandl and many of the men who later described tumors of these bodies. Zuckerkandl demonstrated the same reaction in the periaortic bodies which bear his name. Thus he, Kohn and others believed that these tissues were of common origin and together composed the chromaffin system.

Since Stangl[10] first described a tumor of a Zuckerkandl body, in 1902, I have been able to find reports of only three others in the literature; no other case of concurrent tumors of a carotid body and both Zuckerkandl glands has been reported. For this reason the present case should be of particular interest.

REPORT OF A CASE

History.—A housewife, aged 39, was admitted to the Mayo Clinic on Sept. 13, 1933, complaining of a lump in the left side of her neck. She first noted a small nodule in this region five years previously. For a short time it increased in size, but growth soon became more or less stationary, with only slight fluctuations. There had been no local pain, but since the onset the patient had been annoyed by an almost constant, dull aching pain in the left suboccipital region and in the left side of her neck. Frequent attacks of severe, shooting pain occurred in this region of the neck, extending to the region of the left ear. These attacks lasted only a few seconds, but were often accompanied by a feeling of numbness and dizziness that lasted much longer. The patient's neck was not stiff and she had no difficulty in speaking or swallowing. She had not lost weight. Roentgenologic treatment elsewhere produced no noticeable diminution in the size of the tumor. The only facts of note in her history were that she underwent appendectomy in 1918 and cholecystectomy in 1932.

Physical Examination.—A discrete, firm mass, extending forward beneath the sternocleidomastoid muscle, was found on the left side of the neck just below the angle of the jaw. It measured approximately 3.5 cm. in length and 2.5 cm. in width, and was elevated 1.5 cm. above the normal contour of the neck. The skin was freely movable over it, but the mass was bound down to the underlying structures and could be moved only with difficulty. Moderate pressure on the mass elicited slight tenderness. The nose and throat were normal. The general physical condition was good except for a slight degree of hypertension; the blood pressure was 160 mm. of mercury systolic and 86 diastolic. Urinalysis and all

7. Quoted by Zuckerkandl.[6b]

8. Kohn, A., quoted by Eisenberg and Wallerstein,[23] Zuckerkandl,[6] Rabin[22] and Smith.[11]

9. Stilling, quoted by Smith.[11]

10. Stangl, E.: Verhandl. d. deutsch. path. Gesellsch. **5**:250, 1902.

examinations of the blood gave normal results. In a roentgenogram of the cervical region, the tumor was seen to lie near the surface of the spinal column and did not appear to be attached to it. The exact nature of the mass was questionable, and three preoperative diagnoses were considered, namely, tumor of the carotid body, neurofibroma and mixed cell tumor.

Operation and Course.—A large tumor of the carotid body was found, which measured 5 by 3.5 by 2.5 cm. The common carotid artery and both the internal and the external carotid arteries were surrounded at the point of their bifurcation, so that in removing the mass the common carotid artery had to be ligated and the bifurcation removed. The pathologist reported a malignant tumor of the carotid body with invasion of the capsule.

The immediate postoperative course was satisfactory; no residual signs of injury to the nerves were manifest. However, during the night of the second postoperative day, right hemiplegia developed along with complete aphasia. The following day signs of bronchopneumonia were noted, and death occurred one week after operation.

Necropsy.—On examination of the embalmed body shortly after death, the left middle cerebral artery was found to be thrombosed, with infarction of the left parietal lobe of the brain. The operative site was not disturbed. The heart was normal. Both lower lobes of the lungs were covered with large areas of thick, fibrinous exudate and revealed extensive bronchopneumonia. The appendix and gallbladder were absent. The suprarenal glands and all other abdominal viscera appeared normal. On the right anterolateral surface of the abdominal aorta just lateral to the origin of the inferior mesenteric artery, was a firm, nodular, yellowish-white tumor measuring 3 cm. in length, 2 cm. in width and 1.5 cm. in thickness. It was attached to the aorta by thin strands of fibrous tissue, but appeared to be held in position mainly by numerous branches of the sympathetic nerves which passed along the aorta. The nerve strands entered the substance of the tumor and could not be dissected from it. One surface of this body rested against the inferior vena cava, and when the latter was opened two of the nodules of the tumor were seen to be markedly indenting, although not perforating, its wall. On the left anterolateral aspect of the aorta, mostly caudal to the origin of the inferior mesenteric artery, lay another discrete mass similar in shape to the one on the right side. Its surface, however, was smooth, its color yellowish brown and its consistency soft. It would have been considered a large lymph node except for its consistency and the fact that numerous nerve fibers entered its substance, as they entered the tumor on the right. The mass on the left was slightly smaller than the other, measuring 2.5 cm. in length, 1.5 cm. in width and 0.8 cm. in thickness. Lying in the fatty tissue just below the celiac axis were three small, discrete, bright yellow, spherical bodies of fairly firm consistency. They were each 0.4 cm. in diameter. A few fine nerve fibers were seen to extend to them, but these were torn away when the aorta was removed (fig. 1).

The tumor taken from the neck at operation was grayish white and of firm consistency. It had a slightly nodular surface. Its measurements have already been given. Many fragments of nerve strands were hanging from its surface. The common carotid artery entered the lower pole of the tumor and bifurcated in its substance, so that the internal and external carotid arteries emerged from its upper pole. The cut section also presented a firm, yellowish-white surface.

Histologic Examination.—Tumor of the Carotid Body: Sections from various parts of the cervical tumor were stained with hematoxylin and eosin. Cellular arrangement and density varied widely. In the majority of sections the cells

were arranged in densely packed masses with no particular distribution. However, in a few areas they were much more loosely joined to form whorls and thick strands; these formations were caused by an interlacing network of fine fibrous septums and capillary blood sinuses. The densely packed cells were oval and polyhedral, and gave the impression of being epithelial. In some of these areas the outlines of cells were indistinct, so that the cells appeared to be fused together into large, multinucleated, syncytial masses. The loosely joined cells were almost entirely stellate, with three or four pseudodendritic processes extending from them in various directions and joining with those of other cells, thus forming a ganglion-

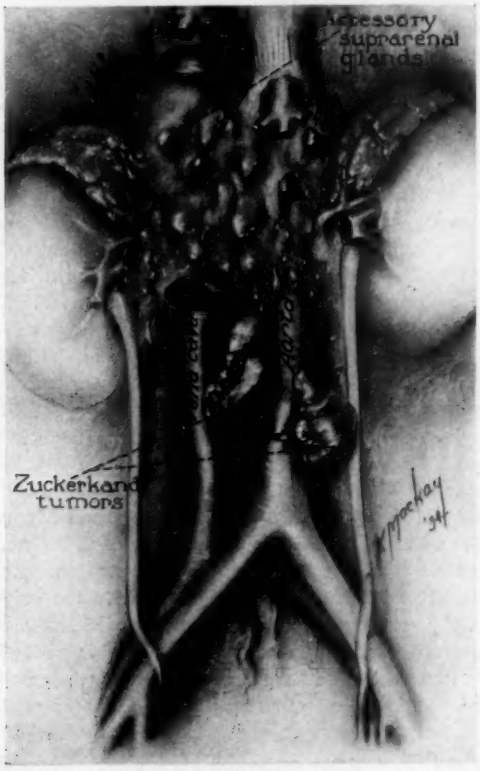


Fig. 1.—Accessory suprarenal glands below the celiac axis and Zuckerkandl tumors on either side of the abdominal aorta.

like network. Between adjoining cell processes in these areas were large, clear spaces, a few of which were lined by endothelium and contained erythrocytes; the remaining clear spaces probably were artefacts due to a shrinkage of cells.

The cytoplasm of the parenchymal cells appeared in two distinct forms: In the larger number it stained homogeneously with eosin, whereas in others it was very pale and contained a deeply staining eosinophilic reticulum. The nuclei varied markedly, in both size and shape; the round and oval types predominated, but there were also a number of large, irregularly shaped nuclei, many of which appeared to be polymorphous. Practically all these nuclei contained hyperchromatic reticulum and not infrequently a small, eccentrically situated nucleolus. Scattered

diffusely and in clumps throughout all sections were large numbers of cells resembling lymphocytes; each consisted of a dark nucleus surrounded by a thin border of cytoplasm. No definite mitotic figures were observed, but the parenchymal cells had invaded the outer capsule in several places (fig. 2*A*).

Tumors of the Zuckerkandl Bodies: In spite of the fact that the two tumors differed in gross appearance, their microscopic structure was essentially the same. Sections were taken longitudinally through the bodies and also from one of the nodules encroaching on the wall of the inferior vena cava. They were stained with hematoxylin and eosin. A definite fibrous capsule was seen, with small fibrous septums extending from it into the substance of the tumor which divided the tissue into irregular lobules. Large numbers of capillary blood vessels, lined with a single

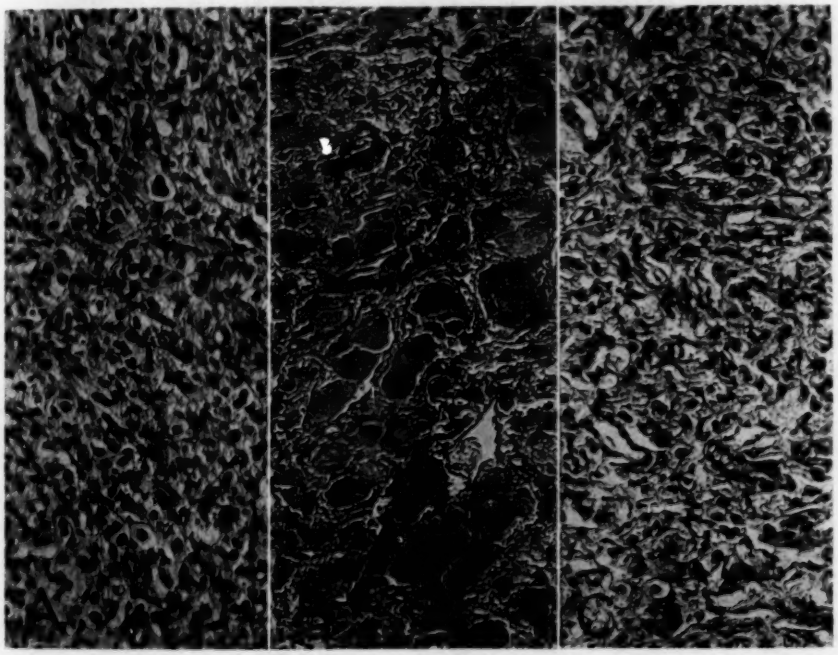


Fig. 2.—*A*, tumor of the left carotid body; *B*, positive chromaffin reaction as demonstrated by the tumor of the right Zuckerkandl body; *C*, tumor of the left Zuckerkandl body.

layer of endothelium and containing erythrocytes, formed an interlacing network. The parenchymal cells exhibited the same features as did those of the cervical tumor, except that the former were densely packed in the peripheral layers and more loosely joined in the central areas. The left periaortic body was less cellular and contained more blood sinuses than did the one on the right, which probably accounted for the fact that it was grossly much softer. The cells had the same polyhedral and stellate shapes, with indefinite outlines and cobweb-like cytoplasm, that were seen in the cervical tumor. However, in those sections fixed in a 5 per cent aqueous solution of potassium dichromate, the cells were clearly outlined and all were oval and polyhedral, the stellate shapes were entirely absent and the cytoplasm stained homogeneously. For these reasons, I believe the stellate

forms to be artefacts produced by the shrinkage of cells. The nuclei of the cells of the Zuckerkandl bodies were round or oval, and corresponded in size to those of the cells in which they were situated. All these nuclei likewise contained hyperchromatic reticulum, and in many there was a small nucleolus. In some, also, was a large, clear vacuole, which gave the nucleus the appearance of a signet-ring. The lymphocyte-like cells found in sections of the cervical tumor were also seen here, although there were comparatively fewer of them; they were distributed separately and in small clumps. An occasional mitotic figure also was observed. The parenchymal cells had invaded the surrounding capsule in several areas and appeared actually to have perforated the wall of the vena cava at one point (fig. 3).

Fig. 3.—Section through the wall of the vena cava, demonstrating the degree of extension of cells of the right Zuckerkandl tumor.

The sections from the three tumors just described were so remarkably similar, histologically, that they could not be distinguished one from the other except by the area of more loosely joined cells in the center of the Zuckerkandl bodies (fig. 2 *B* and *C*).

Accessory Suprarenal Glands: Sections taken from the center of two of the three small yellow nodules which, as already mentioned, were found attached to the anterior surface of the abdominal aorta above the two Zuckerkandl tumors were composed almost entirely of suprarenal cortex with the typical glomerular layer and the fasciculi converging toward the center. A wide reticular layer also was present, with the usual pigment in many of its cells. Situated eccentrically in one section was a small area of basophilic, stellate cells which resembled normal suprarenal medulla. The nodules were without doubt accessory suprarenal glands; one was complete.

Tests for Epinephrine.—The tumor of the carotid body, removed at operation, was preserved for seven days in a solution of formaldehyde, U. S. P. (1:10). From various regions in this mass sections ⅛ inch (0.32 cm.) in thickness were taken, and extracts were made by macerating each in 6 cc. of distilled water, precipitating the protein with trichloracetic acid and filtering. Tests for epinephrine were made by adding to half of this filtrate from 2 to 3 minims (123 to 185 mg.) of a 10 per cent solution of potassium ferricyanide and neutralizing with a saturated solution of sodium bicarbonate. Three sections of the tissue tested in this manner gave a negative reaction for epinephrine. Two sections removed from the periaortic tumors were similarly tested and found to contain no epinephrine, even though they had not previously been preserved except for the embalming of the body before necropsy. The other halves of all of the filtrates were tested by the Vulpian reaction, which similarly gave negative results. Unfortunately, the accessory suprarenal bodies were not tested. Sections were taken from the suprarenal glands which contained visibly large amounts of medulla. These sections were analyzed by the same method and proved to give strongly positive reactions for epinephrine. Thus, it is apparent that any appreciable amount of epinephrine in the periaortic tumors at the time of death could not have been entirely destroyed or washed away by embalming.

Tests for Chromaffinity.—Sections similar to those used in the previous tests were placed in a 5 per cent aqueous solution of potassium dichromate for three days. They were then mounted in paraffin and stained with hematoxylin. Sections from the tumor of the carotid body were entirely negative, but those from the periaortic bodies exhibited a strongly positive chromaffin reaction. Cells of the suprarenal medulla reacted much more weakly, but were definitely positive.

COMMENT

As stated previously, the published reports and reviews on the carotid body and its tumors have covered the field so completely that I wish to mention only the theories of the embryologic origin of the gland in order that there may be a better understanding of the reason for its classification in the chromaffin or paraganglionic system: 1. The theory that the carotid bodies are derived from pharyngeal epithelium has generally been discarded, as the cells of the carotid body have been shown to have no similarity to those derived from the third pharyngeal pouch. Smith [11] demonstrated that the glands were derived from primordial nerve cells in this region and not from epithelium. 2. A few still use the term "perithelioma" for tumors of these organs, on the assumption that the bodies are derived from the perithelium or endothelium of the carotid arteries, but most investigators no longer accept this theory, and Smith's work also disproves it. As early as 1902, both Kohn [12] and Zuckerkandl stated that these bodies "do not arise from thick spots on the arteries." Since perithelial or endothelial cells are probably only flattened fibrocytes, cells of the carotid body could hardly have been derived from them. 3. The third theory is that the bodies are derived

11. Smith, Christianna: Am. J. Anat. **34**:87, 1924.
12. Kohn, Alfred: Arch. f. mikr. Anat. **61**:81, 1900.

from the "sympathogonia cells," as described by Kohn in 1903. These cells are of ectodermal origin, and are thought to constitute the anlage of both sympathetic and chromaffin systems. Thus, they may develop into mature ganglionic cells of the sympathetic system, or they may differentiate to form the chromaffin cells of carotid bodies, the medulla of suprarenal glands, the Zuckerkandl bodies and other small paraganglions which are said to lie along the course of the abdominal aorta. Most investigators agree that, morphologically, the carotid body and its tumors are characteristic of the paraganglionic system. The positive chromaffin reaction is also typical. However, Vassale,[13] Aszoda and Paunz,[13] DeCastro,[13] Chase [14] and Christie [15] have never been able to demonstrate the presence of epinephrine in these bodies. The histologic appearance of the cervical tumor in my case closely resembled this type of tissue, but, owing to the fact that it was previously preserved in solution of formaldehyde, I do not feel justified in attempting to compare the negative histochemical results with those in other cases.

As was stated in the introduction, Zuckerkandl noted a similarity between the morphologic character and chromaffin reaction of the periaortic body and those of the medulla of the suprarenal glands. He did not refer to the presence of epinephrine, but Handschin [16] stated that Biedl,[17] Wiesel [17] and Danisch [17] found it in extracts of Zuckerkandl bodies removed from fetuses ranging in age from 6 months to full term. Since the time of this work, many investigators have corroborated Zuckerkandl's findings, but the presence of epinephrine is still questionable. The four reports of tumors of this body are interesting, because each tumor presented certain characteristics of the chromaffin system, although none presented all of them.

Stangl [10] reported the case of a man, 32 years of age, who complained of an abdominal mass which he had first noticed three months previously. At operation, a discrete tumor the size of an apple was found resting on the aortic bifurcation. This mass was identified as tumor of a Zuckerkandl body by its histologic appearance and by a strong chromaffin reaction. No tests were made for epinephrine; the patient's blood pressure remained normal, as it had before operation.

Hausmann and Getzowa [18] (1922) on postmortem examination of the body of a man 54 years of age, who had died of pneumonia, found, incidentally, a tumor the size of a hen's egg attached to the aortic bifur-

13. Quoted by Christie.[15]
14. Chase, W. H.: J. Path. & Bact. **36**:1, 1933.
15. Christie, R. V.: Endocrinology **17**:421, (July-Aug.) 1933.
16. Handschin, Erna: Beitr. z. path. Anat. u. z. allg. Path. **79**:728, 1927.
17. Quoted by Handschin.[16]
18. Hausmann, Max, and Getzowa, Sophie: Schweiz. med. Wchnschr. **52**:911, 1922.

cation. Its histologic appearance was characteristic of paraganglionic tissue, and it also exhibited a strong chromaffin reaction. No actual tests were made to determine the presence of epinephrine but, because the patient had been seen over a period of four years and had shown signs of nervousness, tremor, profuse sweating and pulmonary bleeding, and because a low value for blood sugar had been found on last admission in addition to the findings at necropsy of an enlarged heart and enlarged kidneys, Hausmann and Getzowa felt that epinephrine probably had been produced by the tumor during the patient's life.

Handschin (1928) described the case of a man, 45 years of age, who had died of carcinoma of the stomach. At necropsy, a tumor the size of a plum was discovered at the aortic bifurcation. It was histologically similar to the chromaffin tumors previously described, but gave no chromaffin reaction, even though the tissue was placed in fixative as short a time as three hours after death. However, an extract of the tissue dilated the pupil of an isolated frog's eye, and this was considered a positive test of epinephrine.

Nordmann and Lebküchner [19] (1931) reported two cases of paraganglionic tumors; only one of these, however, can be classed definitely in this series. A man, 53 years of age, had been killed in an accident. At necropsy, a tumor the size of a kidney was found at the aortic bifurcation. It had the typical histologic appearance of paraganglionic tissue, but the chromaffin reaction was so questionable that the authors considered it to be negative. After two months' preservation in solution of formaldehyde, the tumor was tested for epinephrine; the Vulpian reaction was positive, but the iodine and mercury sublimate reactions were negative. A positive result was obtained when the extract was tested on the isolated heart and eye of a frog. This they believed to be good evidence that the tumor was definitely a chromaffinoma, and they stated further that from their findings it was evident that a positive chromaffin reaction was not necessary so long as the presence of epinephrine could be proved.

The tumors of the Zuckerkandl bodies in the case reported in this paper were equally interesting because they displayed the two most common characteristics of paraganglionic tissue: a typical histologic appearance, and a positive chromaffin reaction. However, this is the only instance in which this type of tumor has produced a positive chromaffin reaction and, also, has been definitely analyzed for epinephrine and found to contain none.

---

19. Nordmann, Martin, and Lebküchner, Eberhard: Virchows Arch. f. path. Anat. **280**:152, 1931.

Taking all these results into consideration, the question arises as to the relation of epinephrine to chromaffinity.

Biedl [7] and Wiesel,[20] at the beginning of this century, stated that extracts of pure chromaffin tissue, when injected into animals, raised the blood pressure. This they believed to be due to the action of epinephrine. Further, they said that if the tissue was exhausted of its secretion by overstimulation of the splanchnic nerves, it no longer raised the blood pressure or exhibited the chromaffin reaction. Therefore they concluded that epinephrine was the substance stained by the chromium salt. A number of investigators (Kohn,[21] Suzuki and Herde,[3] Rabin,[22] Eisenberg and Wallerstein,[23] Maximow,[24] Gérard, Cordier and Lison,[25] Stoerk and von Haberer,[26] Lucien and Parsiot [27]) have stated that the chromium salt is reduced by epinephrine and deposited as an insoluble compound in cells containing epinephrine. Recently (1932), Rogoff [28] summarized this association when he expressed the view that, in general, the chromaffinity of a tissue appeared to be roughly proportional to its content of epinephrine. However, he immediately qualified this statement by saying that in some cases the chromaffin reaction was weak or absent when the epinephrine content was high, and that there had never been any satisfactory demonstration of a reduction in chromaffinity after prolonged splanchnic stimulation during which time epinephrine was secreted in large amounts. This was borne out by the results in the case reported here in which the suprarenal medulla contained an abundance of epinephrine, but evidenced a weak chromaffin reaction. Added to this is the fact previously referred to, namely, that epinephrine never has been detected in the carotid body. Further, the histochemical findings in the reported cases of tumors of the Zuckerkandl body, including the case reported here, have never disclosed the simultaneous occurrence of the chromaffin reaction and epinephrine in the same tumor. Therefore, I am inclined to believe that the widely accepted theory of reaction between these two compounds is incorrect

20. Wiesel, J.: Virchows Arch. f. path. Anat. **176**:103, 1904; Anat. Hefte **19**: 481, 1902.

21. Kohn, Alfred: Ergebn. d. Anat. u. Entwcklngsgesch. **12**:253, 1902.

22. Rabin, C. B.: Arch. Path. **7**:228, 1929.

23. Eisenberg, A. A., and Wallerstein, H.: Arch. Path. **14**:818, 1932.

24. Maximow, A. A.: Textbook of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 704.

25. Gérard, P.; Cordier, R., and Lison, L.: Compt. rend. Soc. de biol. **105**:876, 1930.

26. Stoerk, O., and von Haberer, H.: Arch. f. mikr. Anat. **72**:481, 1908.

27. Lucien, Maurice, and Parsiot, J. V.: Glandes surrénales et organes chromaffines, Paris, Société d'études scientifiques et médicales, 1913.

28. Rogoff, J. M.: The Suprarenal Bodies, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1933, vol. 2, p. 871.

and that they are not related. If this is true, one is forced to accept one of two conclusions: Either the carotid and Zuckerkandl bodies and tumors of these bodies belong to the chromaffin system and the presence of epinephrine is not essential to the diagnosis, or it is essential, and none of the carotid bodies and only a few of the Zuckerkandl bodies may be so classified. A greater part of the existing evidence, therefore, favors the former conclusion, and this is further substantiated by the fact that in the case reported here the concurrence of tumors of both of these glands points toward a common ground of origin and development.

SUMMARY

A case has been described of concurrent tumors of the left carotid body and both Zuckerkandl bodies. The similarity of their histologic appearance to that of paraganglionic tissue associated with the positive chromaffin reaction of the tumors of the Zuckerkandl bodies classifies them in the paraganglionic system. However, they were analyzed for epinephrine and found to contain none. Four other cases of tumor of the Zuckerkandl body have been reviewed and in none have a positive chromaffin reaction and a positive test for epinephrine occurred simultaneously. Also, these two factors have been found to be inconsistent in examination of the suprarenal medulla, and the presence of epinephrine has never been demonstrated in the carotid body. Therefore, I am inclined to believe that there is no definite association between the chromaffin reaction and epinephrine, and the presence of epinephrine is not essential in the classification of a tissue as a part of the paraganglionic system.

RHINO-ENCEPHALOCELE

JEFFERSON BROWDER, M.D.
AND
J. ARNOLD DE VEER, M.D.
BROOKLYN

The following is a report of an unusual form of encephalocele in which the extracranial brain tissue apparently represents a developmental anomaly of the rhinencephalon. The resemblance of this lesion to the so-called nasal glioma will be pointed out. The case also presents certain of the features of tuberous sclerosis.

REPORT OF A CASE

History.—H. V., a new-born female infant, was admitted to the service of Dr. Cameron Duncan on Dec. 25, 1931. The baby had been born at home and was brought to the hospital because of a tumor mass attached to the front part of the head.

She was the third child of normal parents. The other two children were living and showed no congenital abnormalities. No neuropathic heredity could be established from the history. The infant weighed 3,030 Gm. She appeared to be normally developed except for a tense, lobulated, bluish mass attached by a broad pedicle in the midline of the forehead at the base of the nose (fig. 1). The anterior aspect of the mass consisted of three domelike projections covered with thin bluish skin. Over the remainder of the mass and over the pedicle the skin covering was much thicker. By pressure the tumor could be partially reduced, only to refill immediately when the baby cried. The pedicle was firm, and no cranial opening could be palpated.

Examination with roentgen ray revealed a circular bony defect approximately 2 cm. in diameter in the midline just between the medial ends of the superciliary ridges. Otherwise the cranial bones appeared normal.

For four days the infant took its formula well. On the fifth day the temperature rose to 102 F.; the respirations became rapid, and physical signs of bronchopneumonia appeared. The clinical course was downhill until death on the seventh day. The clinical diagnosis was meningo-encephalocele and terminal bronchopneumonia.

Autopsy.—At autopsy the diagnosis of bronchopneumonia was confirmed, and a congenital defect of the interventricular septum of the heart was also found. Dr. W. W. Hala permitted us to use the encephalocele.

The tumor protruding from the frontal region of the head presented a different appearance from that noted during life. It was about one third as large; the lobulations were less definite; its skin covering was wrinkled, and its remaining contents could no longer be reduced. The mass was definitely pedunculated, being attached by a short thick pedicle in the midline of the forehead between the supra-orbital ridges.

From the Departments of Surgery and Pathology of the Long Island College of Medicine.

A cutaneous incision was made about the base of the pedicle, disclosing a smooth-rimmed cranial defect. Thereupon the scalp was reflected by a midline incision and the skull opened by separating the cranial bones at the suture lines. On exposing the cerebral hemispheres a stalk of tissue was found connecting the inferior aspect of the frontal lobes of the brain with the extracranial mass. The dura, which passed through the bony defect, was incised to permit removal of the brain, the tumor and the connecting pedicle en masse.

Following the removal of the brain the dural covering of the anterior fossa was found to be smooth with no prominence in the region of the crista galli, no olfactory grooves and no perforations for the passage of the olfactory filaments. After the dura had been stripped away the cribriform plate of the ethmoid bone presented a smooth cartilaginous surface. Neither the intracranial cavity nor the region of the cranial defect communicated with the nasal cavities.

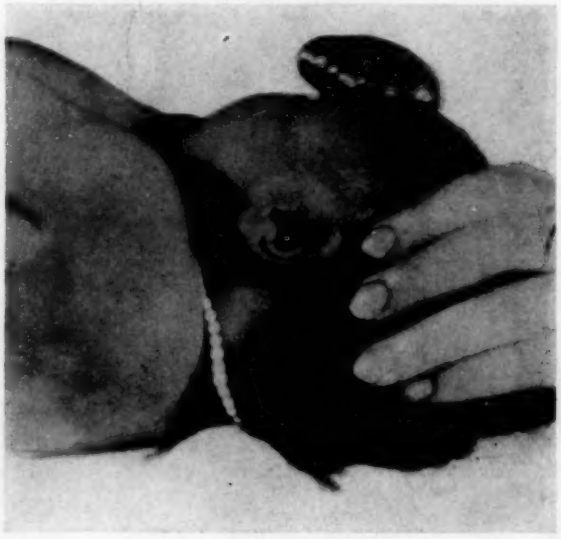


Fig. 1.—The infant shortly after birth. The tense lobulated mass is seen attached to the base of the nose.

After fixation in solution of formaldehyde the tumor measured 3.5 by 4 by 4 cm. It was firm and covered with thin wrinkled skin. It was attached to both frontal lobes of the brain by a broad pedicle.

As viewed from the dorsal aspect the cerebral hemispheres appeared grossly normal. The ventral aspect of the frontal region presented an unusual picture, a striking feature being the total absence of the olfactory bulbs and tracts (fig. 2). In their place there was a relatively broad elevated ridge made up of several irregular convolutions which coursed forward into the pedicle of the tumor. This area was covered with thickened pia-arachnoid enclosing large branches of the anterior cerebral arteries which also passed into the tumor. The remainder of the cerebral hemispheres, the brain stem and the cerebellar hemispheres, from this aspect, appeared anatomically normal except for a slight thickening of the arachnoid.

The membranes and the blood vessels were stripped from the frontal lobes and the stalk of the tumor. The arachnoid was found to continue into the tumor proper; in fact, a large nodule of the tumor lay external to this layer (fig. 2). A continuation of the median longitudinal fissure divided the pedicle into two unequal portions, the left portion, consisting of a single convolution, passing into the tumor as a smooth bulbous swelling which somewhat resembled an olfactory bulb. The right portion was formed by several convolutions, the most mesial of which resembled the one on the left side whereas those more laterally placed appeared as irregular prolongations of the orbital gyri. The latter convolutions were unusually small and numerous, becoming progressively smaller toward the

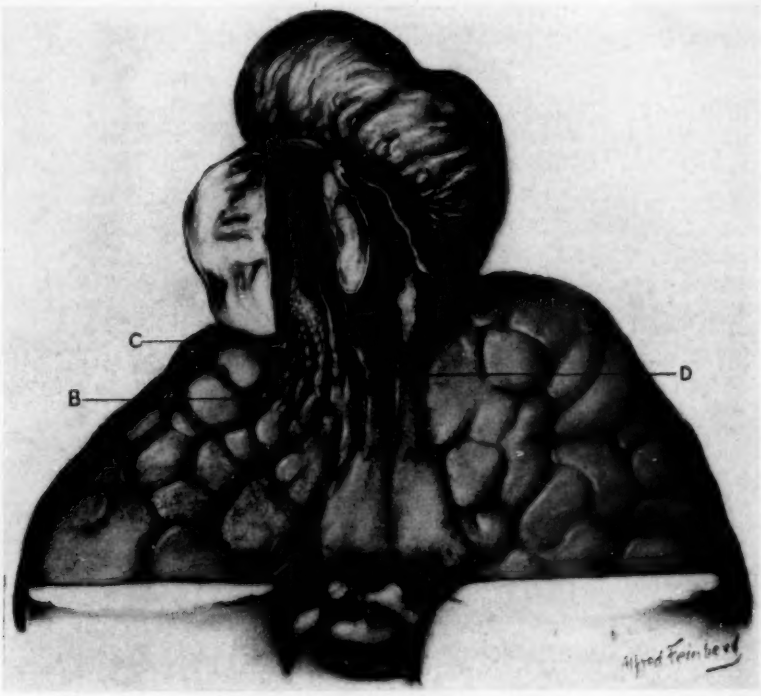


Fig. 2.—Anterior portion of the brain and tumor. The meninges have been stripped away to show: *A*, the absence of olfactory bulbs and tracts; *B*, an area of microgyria in the right orbital gyri and tumor pedicle; *C*, the arachnoid entering the tumor internal to portions of the tumor tissue, and *D*, the median longitudinal fissure.

base of the tumor where they appeared as small closely set nodules. The olfactory striae could not be identified. In this position there was a broad smooth surface bounded laterally by the anterior perforated spaces.

A sagittal section was made through the midline of the brain stem, passing as nearly as possible through the center of the tumor and its pedicle. In the pedicle this section passed somewhat to the right of the median longitudinal fissure, exposing a cavity which communicated with spaces within the tumor (fig. 3).

The structure of the tumor and its pedicle and their relationship to the brain proper can perhaps be described best on the basis of a combined gross and microscopic study, since our original interpretations, based on purely gross anatomic observations, had to be materially revised in the light of subsequent histologic revelations.

The tumor consisted essentially of two cystlike out-pouchings of brain tissue each having a central cavity which communicated, by a separate passage through the pedicle, with the anterior horns of the left and right lateral ventricles, respectively. Each of these pouches was covered with a hyperplastic layer of pia-arachnoid continuous with that of the brain proper. Fragments of dense connective tissue, apparently dura, formed an incomplete investment of both pouches and partially separated them from each other (fig. 4).

From the outer (pial) surfaces of the pouches numerous polypoid outgrowths projected into the pia-arachnoid, and even, through defects in the meningeal coverings, into the subcutaneous layer of the skin. The larger of these polypoid

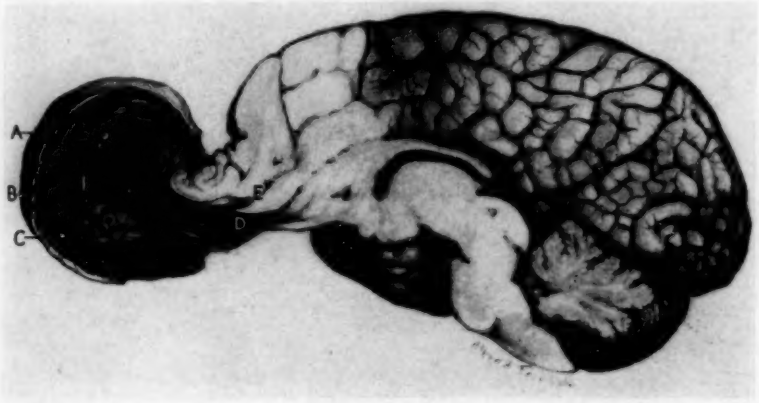


Fig. 3.—Mesial surface of the right hemisphere and corresponding portions of the tumor and pedicle; *A*, pouch of brain tissue; *B*, ependymal-lined cavity; *C*, polypoid structures protruding from the inner surface of the pouch; *D*, canal in the pedicle with its roof formed by *E*, convolutions of the frontal lobe.

structures measured from 0.5 to 1 cm. in average diameter while the smaller ones were of pinhead size or smaller, many being visible only microscopically.

Similar but generally larger polypoid structures projected from the inner (ventricular) surfaces of the pouches, filling their central cavities almost completely.

The portion of the tumor derived from the right hemisphere comprised about three fourths of the entire mass. The polypoid structures in its cavity were firm, of a tan color due to staining with hemoglobin, and for the most part large and smooth-surfaced. Many of them were branched. They had their origin near the neck of the pouch or arose by long narrow stalks from the wall of the cavity within the right portion of the pedicle.

The portion derived from the left hemisphere formed a flattened caplike mass with a small collapsed central cavity. The polypoid growths projecting into this cavity were much fewer and smaller than those found in the right portion of

the tumor. The outgrowths from the pial surface, however, were numerous, and the larger of these measured from 1 to 1.5 cm. in diameter.

The canal in the right portion of the tumor pedicle was relatively large. Its lining inferiorly and laterally was made up of parallel longitudinal folds of brain tissue which streamed forward into the body of the tumor and gave origin to

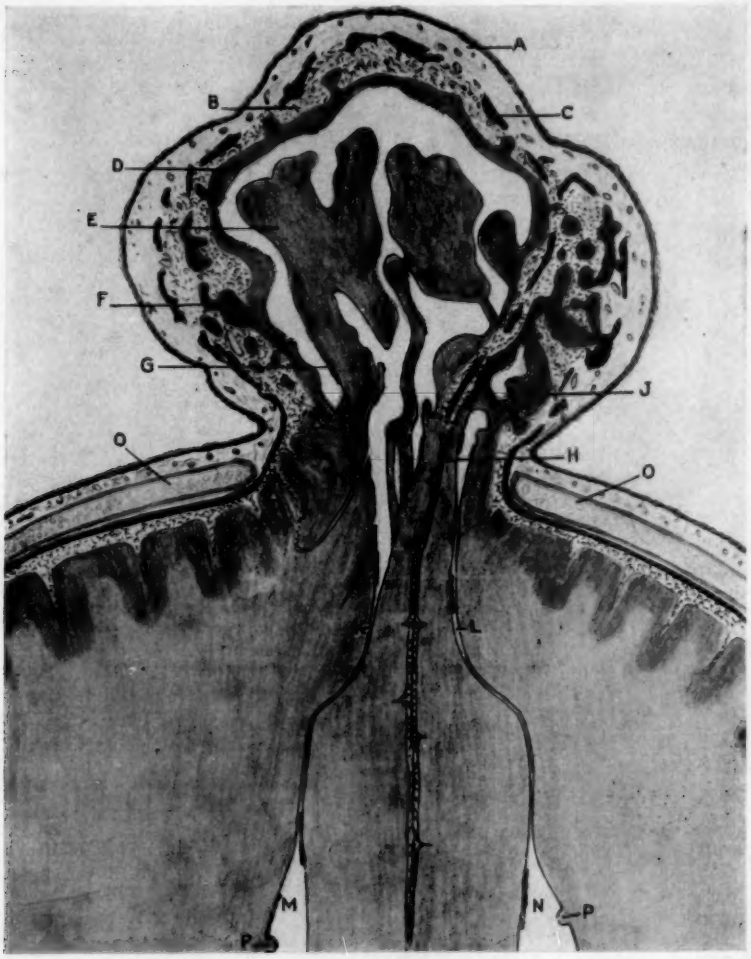


Fig. 4.—Diagrammatic representation, from below, of the encephalocele and its relationship to the cerebral ventricles: *A*, skin covering; *B*, subarachnoid space; *C*, fragments of dura; *D*, pouch of brain tissue derived from the right hemisphere; *E*, polypoid nodules projecting into its cavity and *F*, into the subarachnoid space; *G*, remnants of an ependymal lining; *H*, the median longitudinal fissure; *J*, the left pouch with its cavity and polypoid outgrowths; *K* and *L*, canals through the pedicle leading to *M* and *N*, right and left lateral ventricles; *O*, cranium with the nasofrontal defect, *P*, the subependymal nodules in the cerebral ventricles.

many of the polypoid structures noted. Superiorly the cavity was bounded by convolutions of the frontal lobe devoid of meningeal coverings and drawn forward and flattened so that they terminated in sharp thin edges. Among these convolutions communications could be traced between the ependymal-lined cavity and the subarachnoid space. As the canal traversed the frontal lobe of the brain it narrowed abruptly, curving outward and upward to join the anterior horn of the right lateral ventricle.

A much smaller canal was found in the left portion of the tumor pedicle. It could be traced backward to the anterior horn of the left ventricle.

The mesial aspect of the hemispheres presented various other abnormalities. The anterior portion of the corpus callosum was poorly defined, and the parolfactory area was not recognizable as such. The marginal and callosal gyri appeared drawn forward toward the base of the tumor. Indeed, several atypical convolutions of these gyri entered into the formation of the tumor pedicle and formed the superior wall of the canal in its right portion as noted. The remainder of the brain from this aspect was essentially normal.

Multiple sections in the coronal plane revealed numerous small nodular protrusions on the ependymal surfaces of all ventricles. These were most numerous in the fourth ventricle and in the occipital and temporal horns of the lateral ventricles. They varied from the size of a pinpoint to a diameter of 3 mm. Most of them bulged only slightly into the ventricles while several were pedunculated. They were slightly paler and somewhat firmer than the surrounding brain tissue. A row of small nodules arose from the under surface of the quadrigeminal body, protruding into the aqueduct of Sylvius but causing no apparent obstruction.

Several of the nodules became evident only in stained preparations since they did not protrude into the ventricles and were not distinguishable grossly on the basis of their color and consistency.

We estimated that there were between thirty and forty of these "subependymal" nodules exclusive of similar structures in the extracranial mass and its pedicle.

No discrete nodules or areas of sclerosis could be found in the cortical or subcortical zones of the hemispheres except where they entered into the formation of the encephalocele and its pedicle.

Microscopic study of the right portion of the extracranial mass showed a thin-walled pouch composed of sclerotic brain tissue in which there was a vague differentiation into cortical and medullary zones. The central cavity contained some fairly fresh blood, and its lining surface was superficially eroded so that it appeared rather ragged. In some areas, however, remnants of an ependymal lining could be recognized. The polypoid and nodular protrusions into the cavity were of the same general structure as the wall of the pouch. The outgrowths from the pial surfaces were numerous, and many of them were small. They lay in a richly vascular, thickened pia-arachnoidal layer. Some of them were attached by narrow stalks while others were widely separated from the wall of the pouch and were devoid of any direct attachment to it (fig. 5). (The latter observation was made through a study of drawings from serial sections, made by means of a camera lucida.) In some areas an intermingling of these processes with fibrotic pia-arachnoid suggested an invasive tendency on the part of the tumor tissue.

Fibrillary astrocytes predominated both in the wall of the pouch and in the structures protruding from its surfaces (fig. 6 *C*). Microglial cells were abundant along the eroded surfaces of the tumor nodules and adjacent to scattered small hemorrhages (figs. 6 *A* and *B*). Oligodendroglial cells were also numerous. Many cells could not be definitely identified. Neurons were found in moderate

numbers and showed various forms of degeneration (fig. 6 *D*). In some areas masses of myelinated fibers extended like a fringe from the surfaces of the nodules, and occasional long myelinated fibers could be traced through their substance. The structure of some of the nodular growths suggested central neurinoma.[2]

Fig. 5.—*A*, the wall of one of the pouches with *B*, nodular protrusions into *C*, the hyperplastic pia-arachnoid. At *D* are isolated nodules of the same character (hematoxylin and eosin).

The left portion of the extracranial mass was essentially the same as the right in its microscopic details.

2. This resemblance was pointed out by Dr. Joseph H. Globus with whom we discussed the case and to whom we are indebted for the name "rhino-encephalocele."

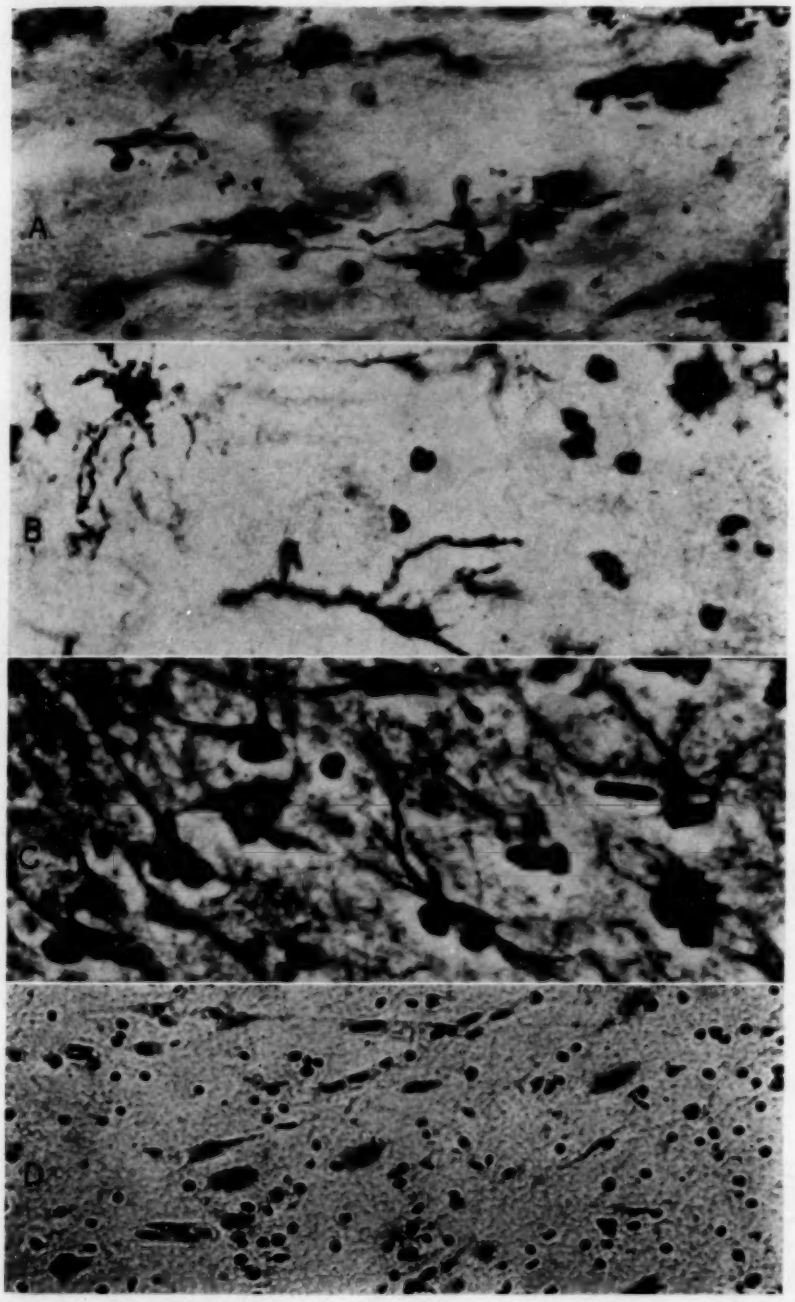


Fig. 6.—Cellular components of the nodules of the tumor, *A* and *B*, microglia (Penfield); *C*, fibrillary astrocytes (Loughlin method), and *D*, neurons (Nissl).

In the pedicle of the tumor an interesting feature was the extreme thinness of the walls of the ventricular cavities. In this region also fragments of ependyma persisted. In the distal portion of the pedicle the brain tissue was markedly sclerotic while more centrally the gliosis was rather closely confined to a zone about the ventricular cavities and merged by a gradual transition with relatively normal surrounding brain tissue.

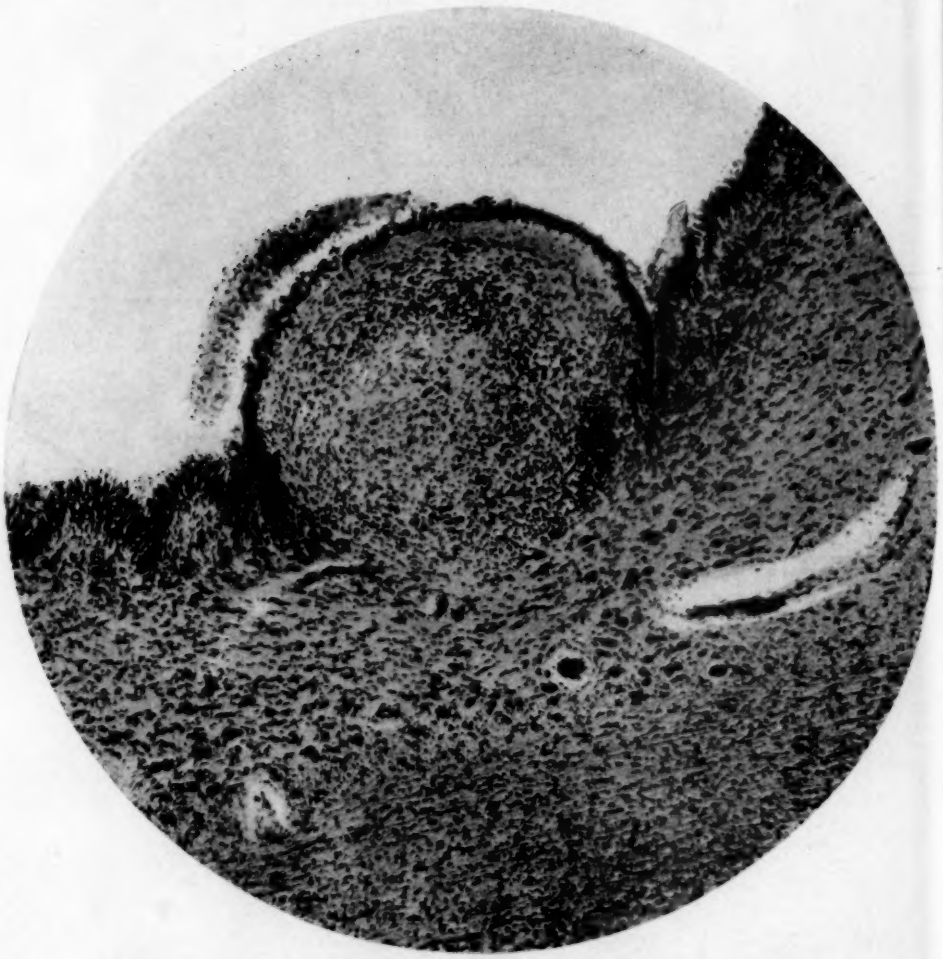


Fig. 7.—One of the smaller of the subependymal nodules protruding into the cerebral ventricles.

The nodules protruding into the ventricular cavities of the brain proper consisted of small discrete cellular areas sharply demarcated from the surrounding white matter. Some were covered on their ventricular surfaces by hyperplastic and irregular ependyma (fig. 7), while others showed eroded surfaces. The nuclei in the nodules appeared round or oval, and no cell bodies or processes could be

demonstrated by the ordinary staining procedures. By means of an apparently new staining method [3] we were able to demonstrate the glial nature of many of the cells. They were predominantly fibrillary astrocytes with smaller numbers of protoplasmic astrocytes, oligodendroglial and microglial cells. No neurons could be recognized. In the adjacent white matter was a zone of compressed nerve fibers with numerous microglial cells.

The anterior horns of both lateral ventricles were collapsed and partially obliterated by gliosis. Many sections from grossly normal portions of the brain showed retarded development in the cortical architecture. Only a slight degree of myelinization could be demonstrated, perhaps owing in part to unfavorable fixation. Frequently neurons were seen in the subcortical white matter. No mitral cells were found either in the neighborhood of their usual location or in the extracranial brain tissue. Sections through the hippocampal gyri showed a suggestion of the characteristic grouping of cells into islets, but the cells appeared fewer and less regularly arranged than usual. The dentate gyri also resembled the normal but were poor in nuclear elements and somewhat atypical in architecture. The cerebellum showed a broad external granular layer.

COMMENT

The case presents as its outstanding features: (1) a meningoencephalocele in which the protruding brain tissue consisted of sclerotic out-pouchings from the inferior portions of the frontal regions of both cerebral hemispheres, (2) an absence of recognizable olfactory lobes, tracts and striae, (3) an absence of perforations in the cribriform plate of the ethmoid and of the crista galli, (4) subependymal nodules scattered throughout the ventricular system, (5) histologically similar nodules protruding from the inner and outer surfaces of the extracranial cerebral out-pouchings, (6) a developmental anomaly in another organ, namely, a defective interventricular septum of the heart.

Grossly the extracranial mass is reminiscent of the rhinencephalon of the lower mammals. We believe that this structure represents an abnormally developed rhinencephalon. Its nodular and polypoid protrusions we interpret as the expression of a blastomatous character acquired by the extracranial brain tissue.

The stage of development of the embryo at which this disturbance must have originated may be roughly estimated as being at least prior to the third month when normally the rhinencephalon is found well differentiated into olfactory bulbs and tracts and the cartilaginous cribriform plate of the ethmoid has already formed around the olfactory nerve fibers. By this time the crista galli is normally represented by a cartilaginous ridge.

The subependymal nodules bear a close resemblance to those found in tuberous sclerosis except for the absence of the characteristic "giant cells." The presence of additional developmental anomalies is also sug-

3. This method which combines features of the Cajal and Bielschowsky procedures will be reported elsewhere by its originator, Dr. E. H. Loughlin.

gestive of tuberous sclerosis. On the other hand, no definite cortical sclerotic nodules were found, and the heterotopic ganglion cells in the subcortical zone were not of the abnormal types described in that condition. We believe, therefore, that this case cannot be considered an example of tuberous sclerosis although many features indicate a relationship to that disease.

We have gathered from the literature reports of about fifty cases in which tissue, more or less resembling brain tissue, has been found subcutaneously at the base of the nose, in the nasal or nasopharyngeal cavity or in both locations. Most of these were evidently instances of congenital malformations and have been variously designated as sincipital or basal hernias of the brain, encephaloceles, encephalomas, gliomas or fibrogliomas.

From an anatomic standpoint the lesions, which are most frequently referred to as hernias of the brain or encephaloceles, may be divided into sincipital and basal types. According to von Meyer [4] there are three subdivisions of the former:

1. Encephalocele nasofrontalis, in which the pedicle passes through a cranial defect located at the junction of the nasal and frontal bones. In such cases the tumor is externally visible in the midline at the base of the nose.

2. Encephalocele naso-ethmoidalis, in which the bony defect is between the frontal, nasal and ethmoid bones, and the tumor appears externally in the neighborhood of the junction of the bony and cartilaginous portions of the nose.

3. Encephalocele naso-orbitalis. In this instance the cranial defect lies between the frontal, nasal and lacrimal bones. The tumor enters the orbit, appearing at or near the inner canthus of the eye.

As Fenger [5] has noted, the naso-ethmoidal and naso-orbital varieties are not easily distinguished from each other since they leave the cranium at about the same place.

Basal encephaloceles, sometimes considered a subdivision of sincipital encephaloceles, are distinguished from the foregoing types by forming tumors not usually visible on the face. Of these Heinecke [6] described three forms:

1. Encephalocele sphenopharyngealis, which leaves the cranium between the body of the sphenoid and the ethmoid bone and extends into the nasal or nasopharyngeal cavities or even into the mouth.

2. Encephalocele spheno-orbitalis, which leaves the cranium through the superior orbital fissure to enter the posterior portion of the orbit.

4. von Meyer, Edward: Virchows Arch. f. path. Anat. **120**:309, 1890.

5. Fenger, Christian: Am. J. M. Sc. **109**:1, 1895.

6. Heinecke, W., quoted by Fenger.[5]

3. Encephalocele spheno-maxillaris which passes through both the superior and the inferior orbital fissures into the spheno-maxillary fossa. "The tumor can be felt in the mouth on the medial side of the ascending ramus of the inferior maxilla, and is visible on the outside of the face, on the cheek below the zygoma, in the same place where the retro-maxillary branches of retro-nasal fibroids present" (Fenger [5]).

It seems possible that the rhinencephalon may be the portion of embryonal brain particularly concerned in the formation of encephaloceles in any of these locations. Our review of reported cases, however, has not included the many instances of orbital encephalocele, since these seem less likely to be genetically similar to the case here reported.

We recognize that in the large group of cases which we have reviewed the structural characteristics of the extracranial tumors are widely varied. In 1890 Berger [7] observed:

> The structure of the nerve tissue which enters into the formation of certain encephaloceles departs notably from the type of the normal brain parts from which the tumors are derived. Because of this circumstance and the modifications in their meningeal envelops they ought to be considered as true neoplastic products to which the name encephaloma should be given.

Von Meyer [4] reported as an instance of basal hernia of the brain the case of an infant with an intranasal polypoid growth composed of solid glial tissue. The tumor was attached to the brain by a stalk which passed through an opening in the ethmoid bone. Fenger [5] reported the successful extirpation of a similar intranasal growth which he likewise called a basal hernia. In fact, most of the older records of cases of this general nature appear under the designation of hernias of the brain, although in many instances the herniated tissue showed definite blastomatous characteristics.

Extranasal or intranasal growths of this character have been called gliomas by Schmidt,[8] Clark [9] and Sussenguth,[10] and fibrogliomas by Rocher and Anglade,[11] while Terplan and Rudofsky [12] pointed out the resemblance of an intranasal growth to neurinoma.

Among the cases reported as encephalocele are many in which there were marked blastomatous characters. The cases of Schötz,[13] Guthrie and Dott,[14] Natanson [15] and Malek [16] fall into this group.

---

7. Berger, Paul: Rev. de chir., Paris **10**:269, 1890.
8. Schmidt, Martin B.: Virchows Arch. f. path. Anat. **162**:340, 1900.
9. Clark, Payson: Am. J. M. Sc. **129**:769, 1905.
10. Sussenguth, L.: Virchows Arch. f. path. Anat. **195**:537, 1909.
11. Rocher, H. L., and Anglade: Rev. de chir., Paris **62**:147, 1924.
12. Terplan, K., and Rudofsky, F.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **14**: 260, 1926.
13. Schötz, W.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **58**:137, 1909.
14. Guthrie, D., and Dott, N.: J. Laryng. & Otol. **42**:733, 1927.
15. Natanson, Leo: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **135**:103, 1933.
16. Malek, S. A.: J. Anat. **66**:264, 1932.

Berblinger,[17] reporting a case of glioma at the base of the nose, suggested the possibility of a developmental relationship to the olfactory bulb. Terplan and Rudofsky[12] accepted Berblinger's theory so far as the structure of the tumor in their case permits of this possibility. In both instances, however, no confirmation of this idea was possible.

An isolated instance in which there was definite evidence of a relationship between the olfactory bulbs and "an encephalocele in the nasal region" has been reported by Malek.[16] The case was that of a new-born infant with a large pear-shaped tumor situated in the midline of the face, extending from the middle of the forehead to the upper lip. The encephalocele, evidently belonging to the naso-ethmoidal group, was covered by dura and skin, contained ependyma-lined cavities and was attached to the brain by a pedicle passing through a cartilaginous tube. Within the cranial cavity the pedicle divided into left and right portions, each of which was attached to the inner margin of the corresponding olfactory bulb. The extracranial mass was described as a glioma. The author concluded: "The tumor is of cerebral origin and appears to be a protrusion from that part of the neural tube which gave rise to the olfactory bulbs. This is indicated by its connection with the latter and by the ependymal-lined cavities contained in it."

That other reported encephaloceles in this region may have been derived from the rhinencephalon seems highly probable, but we have been unable to find any other case presenting sufficient evidence to establish this relationship. On the other hand, it seems even more probable that not all such tumors were "rhino-encephaloceles." But the evidence in support of this statement is also unsatisfactory, for in only a few instances has the condition of the olfactory bulbs been recorded. Even in the reports of encephaloceles leaving the cranium through a defective lamina cribrosa the olfactory bulbs almost invariably are not mentioned.

We have recently reexamined the tissue from a case reported by one of us (Browder[18]) and found a striking similarity to the tumor in the case reported here. A brief summary of this case will serve to emphasize this resemblance.

L. V., an infant, aged 11 months, showed a nodular mass "about the size of an English walnut" at the base of the nose in the midline. A previous attempt at removal of the mass had been abandoned because of excessive hemorrhage. Examination with roentgen ray showed "a circular bony defect in the region of the glabella." At operation the mass was freed from below upward until a stalk was identified which led through the small bony opening in the skull. The opening was enlarged; the dura was incised, and the stalk was seen to divide into two portions, the larger part being attached to the right frontal lobe, the lesser to the

17. Berblinger, quoted by Terplan and Rudofsky.[12]

18. Browder, J.: Ann. Otol., Rhin. & Laryng. **38**:395, 1929.

left. Both attachments were divided. There was no evident communication with the ventricles. The postoperative course was good for the first twenty-four hours; then bronchopneumonia developed, and the child died. There was no evidence of meningitis. Permission for an autopsy was refused. The excised tissue contained a soft, grayish-white central mass from which smaller nodules of similar consistency extended into the surrounding vascular connective tissue. The free surface was covered with normal skin. The microscopic sections showed a structure almost identical with portions of the tumor in H. V. (fig. 5).

In this case as in many others in the literature the possible derivation of the tumor from the rhinencephalon remains a matter of speculation.

CONCLUSION

The case of an infant with an unusual type of nasofrontal encephalocele which we interpret as a developmental anomaly of the rhinencephalon is recorded. The blastomatous features of the encephalocele are regarded as secondary characteristics such as have been indicated in previous reports by the names "nasal glioma," "encephaloma" and "fibroglioma." We have used the designation "rhino-encephalocele" to indicate the origin and essential nature of the lesion.

The presence of certain of the features of tuberous sclerosis suggests a genetic relationship between the two processes.

STUDIES IN ATHEROSCLEROSIS: CHEMICAL, EXPERIMENTAL AND MORPHOLOGIC

III AND IV. RÔLES OF CHOLESTEROL METABOLISM, BLOOD PRESSURE AND STRUCTURE OF THE AORTA; THE FAT ANGLE OF THE AORTA (F.A.A.), AND THE INFILTRATION-EXPRESSION THEORY OF LIPOID DEPOSIT

SOL ROY ROSENTHAL, M.D., PH.D.
CHICAGO

III. RELATIONSHIP OF PHYSICAL CHEMICAL CHANGES IN THE AORTA TO INCLINATION TO ATHEROSCLEROSIS (F.A.A.)

The problem of determining abnormal states in the aortic wall is difficult. The difficulty becomes more acute when one considers that the normal changes occurring in this vessel are not definitely established.

The two great factors that may alter the structure of the aorta are age and blood pressure. Endowment, naturally, forms the basis from which these components must be measured.

A. THE RELATIONSHIP OF AGE AND THE INTERNAL ELASTIC MEMBRANE TO THE LIPOID DEPOSIT IN THE AORTA

Age.—The important alterations of the aorta with age are given as changes in the interstitial substance and elastic lamellae which finally lead to a dilatation of the vessel.

The Interstitial Substance: The nature of the interstitial substance and the elastic fibers of the aorta has given a subject for much discussion. The connection between the elastic fibers and the interstitial substance is not well understood, but Benninghoff has shown that the interstitial substance appears before the elastic fibers, and that the latter, when developed, are contained in the former, thus forming one continuous sheet. The latter is impregnated with numerous channels for drainage.

With increasing age the amount of the interstitial substance is reported to be increased (Bjorling, Schultz, Ssolowjew,[a, b] Cellina). This probably means that the increase is only relative, as the elastic fibers decrease (Benninghoff). Although it was at first thought that this augmentation was the underlying factor in the development of atherosclerosis, it was later established that it was physiologic and was found in old persons without atherosclerotic changes of the aorta (Björling, Schultz, Ssolowjew,[a, b] Cellina). That this substance does alter with age as do all aging colloids (Wells), and that it then has an affinity for fat and calcium, are universally admitted (Aschoff,[d]

Wells, Okunoff). Whether this depends on the changed colloid state or whether it is related to the increased acidity (Schmidtmann and Huttich) is unknown. That it is not the only factor involved in atherosclerosis has been clearly shown by Björling, Schultz, and others.

The Internal Elastic Membrane: The intima at birth is negligible but soon after develops rapidly into three layers: an inner fibrous layer, a middle fibro-elastic layer bounded distally by an external limiting membrane, and an outer fibromuscular layer terminated by the internal elastic membrane (Key-Aberg, Grundstein, Jores, Voigt, A. Aschoff).

According to A. Aschoff, this development reaches its peak at about 33 years (ascending stage of life). From then on there is a stationary period until 45 years, after which degenerative changes begin (descending stage of life).

The cause of this hypertrophic, hyperplastic development of the aortic intima and its relation to atherosclerosis have been greatly disputed points. Many authors believe that it is secondary to the irritation caused by the lipoid deposit (Anitschkow [b, c]), which occurs from birth onward.

Against this hypothesis are numerous facts. The lipoid deposits in youth, although to be found in the same sites as the atherosclerotic lesions (Zinzerling [a]), are not uniform and are most pronounced in the thoracic portion of the aorta. Yet, in a series of microscopic studies of human aortas, the development of the fibro-elastic layer in the abdominal portion was found to be much more pronounced than that in the thoracic portion. In the latter the fibro-elastic layer was about one-third to one-fourth as wide as in the former (figs. 3*A* and *B*).

The fat deposit was found to be in no way parallel to the proliferation of the internal elastic membrane. The fat deposit early in life was very slight, while the proliferation was extensive (Görög). In 11 of 28 cases Görög found that there was no lipoid in the internal elastic membrane under 20 years.

Experimentally in rabbits no proliferation of the elastic fibers was found after one hundred and twenty days of feeding cholesterol (0.5 Gm. in 10 cc. of linseed oil daily). Anitschkow [c] and Ssolowjew,[c] Stuckey, McMeans [b] and Wolkoff [b] reported elastic fiber increase after about six months of feeding, but, as Wolkoff [b] brought out, the animals in which these changes occurred were old ones.

According to Benninghoff, the structure of a vessel is dependent on the circulatory demands made on it and not on its endowment. Görög compared the increase in the volume of the blood with the size of the aorta from birth to adult life, and found that there was a great disproportion between the two. At birth the volume of blood is from 350 to 400 Gm., and in adult life it is from 5,000 to 6,000 Gm. The diameter

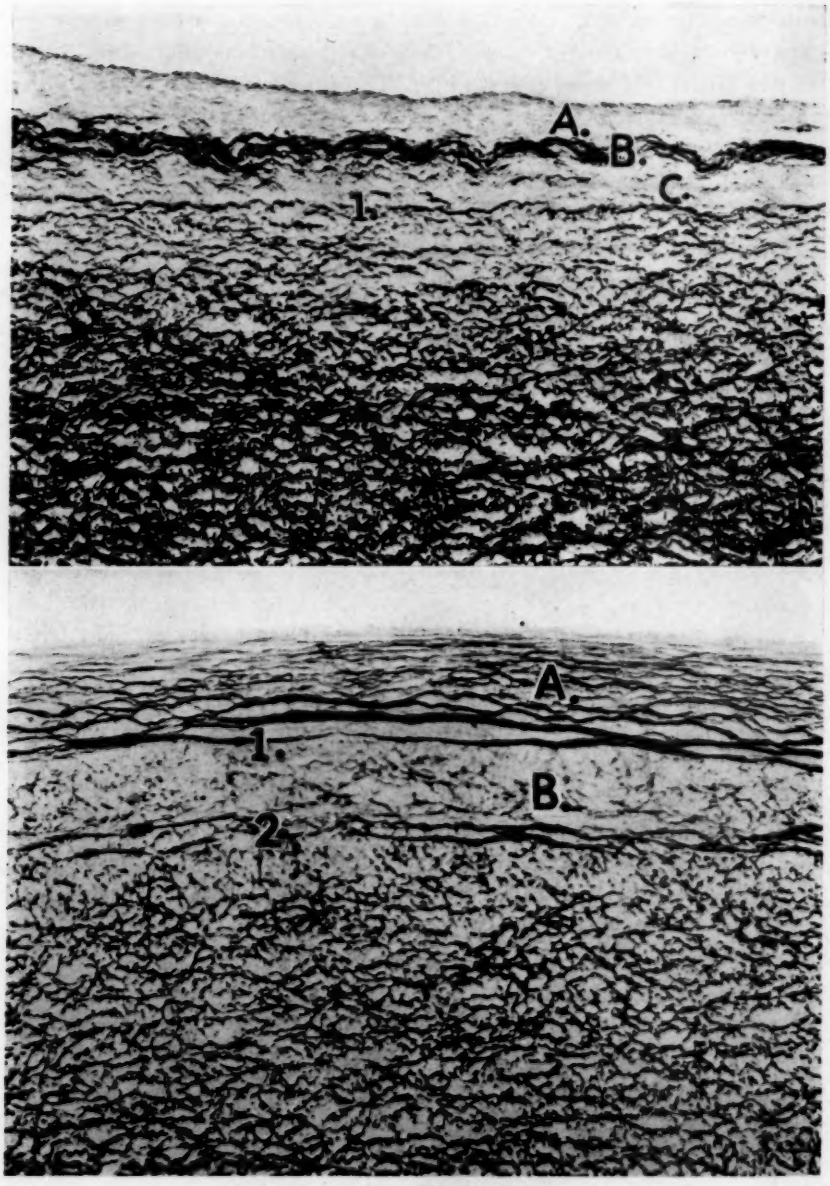


Fig. 3.—Aorta of a 35 year old normal woman: The upper half shows the ascending portion of the aorta, in which *A* indicates the fibrous layer, *B* the fibro-elastic layer, *C* the fibromuscular layer and *I* the internal elastic membrane. The lower half shows the abdominal portion in which *A* indicates the fibro-elastic layer, *B* the fibromuscular layer, *1* the external limiting membrane and *2* the internal elastic membrane. (Weigert's elastica stain; × 100.)

of the aorta varies from 0.77 to 3.69—3.85 cm. (female and male, respectively), while the thickness varies from 1.17 to 1.71—1.84 mm. (male and female, respectively). He concluded that the size of the aorta, especially the thickness, cannot keep pace with the increase in blood volume.

The determination of the varying demands made on the aorta is best seen by its increase in size. Both the width and the thickness increase with age, the thickness increasing at the expense of the intima (Kani). Although the width of the aorta varies somewhat with the length of the body (Scheel), when a large group of cases is considered this difference is compensated for.

TABLE 22.—*The Measurements of the Aorta of the White and Colored Races from Birth to 30 Years of Age*

	White								Colored							
	Male				Female				Male				Female			
	Measurements, Mm.*				Measurements, Mm.				Measurements, Mm.				Measurements, Mm.			
Age	Cases	1st	2nd	3rd	Cases	1st	2nd	3rd	Cases	1st	2nd	3rd	Cases	1st	2nd	3rd
0–1	65	25.5	16.6	12.4	45	25.7	15.8	11.4	55	24.1	16.1	11.0	54	25.6	16.5	12.3
2–5	43	37.0	22.6	16.8	31	35.6	21.7	15.9	47	37.0	24.1	16.7	42	36.0	22.2	15.9
5–11	40	42.3	25.5	19.4	23	41.5	25.5	18.4	30	43.0	27.4	19.0	19	40.0	26.7	19.7
11–15	23	50.4	31.6	25.1	13	50.2	29.0	21.8	11	46.4	31.4	22.3	15	45.5	28.8	19.4
16–20	30	56.4	35.8	26.9	20	52.3	33.8	24.3	16	54.9	38.4	27.4	23	50.0	32.3	25.0
21–30	41	58.0	38.2	30.3	29	55.2	35.9	28.1	31	61.5	39.5	29.9	53	55.7	36.0	28.2
% increase		127	130	150		115	125	155		155	151	173		117	110	130

* The first measurement was above the aortic cusps, the second at the diaphragm and the third at the bifurcation at the aorta.

Table 22 presents the measurements of the aorta from birth to 1 year up to 30 years for both sexes and races. The three measurements of the aorta given were determined by a firm rule in the following locations: 1 cm. above the aortic cusps (first), at the diaphragm (second) and at the bifurcation of the aorta (third).

For both races and sexes there was practically no difference in the size of the aorta up to 11 years (also found by Rössle for both sexes of the white race). From then on the female aorta remained somewhat smaller in its second and third measurements, and from 16 years onward the first measurement also remained smaller. This is a clear demonstration of the effect of demand on the size of the aorta, as the young girl after 11 years is less active physically than the boy.

In comparing the increase in the ascending portion with that in the abdominal portion of the aorta there was usually about a 25 per cent increase of the latter over the former. This difference was probably due to the greater physiologic demands made on that part of the aorta and

may account for the difference in the development of the intima (Aschoff,[f] Jores, Benninghoff, Kani).

The thickness of the entire abdominal portion of the aorta also increases to a greater extent than that of the thoracic part. Kani showed that the ascending aorta increases in thickness from birth to 2 years up to 30 years, 49 and 29 per cent, respectively, for male and female. At the diaphragm this increase is 71 and 54 per cent, respectively, and at the bifurcation of the aorta 62 and 51 per cent, respectively.

What relationship there is between this fully developed intima and the lipoid deposition that follows has been much debated. Following the revival of the imbibition-infiltration theory of Virchow by Aschoff,[e] this concept has received recognition everywhere (Ribbert, Hueck, Jores, Anitschkow,[a] Petroff, Glasunow, Hackel, Lange[a]).

One of the objections to this theory as it stands is that the lipoid in the serum as well as the arterial pressure is similar in the entire arterial tree including the arterioles (Lange[c]), yet the lipoid deposit is found mainly in the elastic type of arteries (aorta, pulmonary, coronary and carotid arteries), where the internal elastic membrane is poorly developed. Rarely is fat found in the muscular arteries, where the internal elastic membrane is well developed (Hesse, Lotzmann, Nordmeyer).

Why this difference should exist has not been made clear, for if the internal elastic membrane acted as a barrier to the infiltrating lipoid from the blood plasma, one would expect lipoids to be deposited in the muscular arteries also.

A plausible solution of this problem was seen in the arteries of the cholesterol-fed rabbits which received 0.5 Gm. of cholesterol dissolved in linseed oil daily for one hundred and twenty days.

First, the normal histology of the rabbit's aorta must be considered (fig. 4 *A*). The intima consists of a layer of endothelium and a few fibrous and elastic fibers. There is no definite internal or external elastic membrane, and the media is rich in elastic fibers and, to a less extent, muscle fibers. The adventitia is insignificant. The peripheral vessels, as in man, are muscular and have a pronounced internal elastic membrane (fig. 4 *B*).

After feeding cholesterol, a deposit of lipoid readily occurred in the rabbit's aorta as well as in the pulmonary artery, but only rarely were the muscular arteries involved. In the aorta as in the pulmonary artery the lipoid deposit first occurred free beneath the endothelial lining, causing the intima to become wider. Later the deposit extended between the elastic fibers of the inner media. The fat deposit, however, instead of being found on the proximal aspects of the elastic fibers, was usually found on the distal aspects. In other words, although the cholesterol esters unquestionably filtered into the wall with the blood serum, there was probably an attempt to express the latter with contraction of the

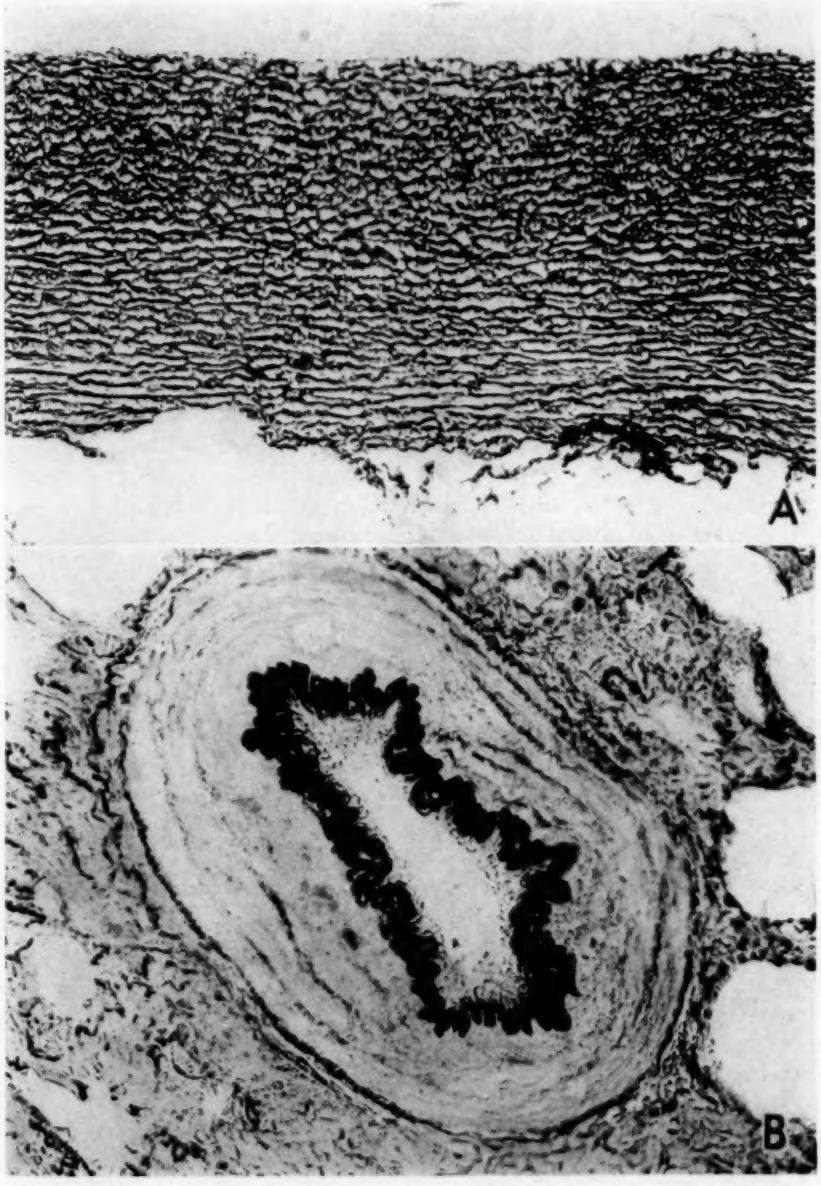


Fig. 4.—*A*, normal rabbit's aorta. Note the insignificance of the intima, the internal and the external elastic membranes. (Weigert's elastica stain; × 150.) *B*, muscular type of artery in the rabbit showing the well developed furrowed internal elastica membrane. (Weigert's elastica stain; × 75.)

vessel. To further substantiate the possibility that a definite attempt was made by the elastic tissue to express the infiltrating lipoids, the peripheral vessels were examined. As has been stated, these vessels have a pronounced internal elastic membrane. Lipoid-staining material was found in the lumens of these vessels (fig. 5), but the intima only rarely showed lipoid deposit. In one such vessel a diffuse cholesterol deposit was found, whereas similar arteries in the vicinity were lipoid-free.

An examination of the internal elastic membrane of the latter vessel revealed that for some reason it had given way, and the fragments were displaced away from the lumen by the infiltrating cholesterol-laden

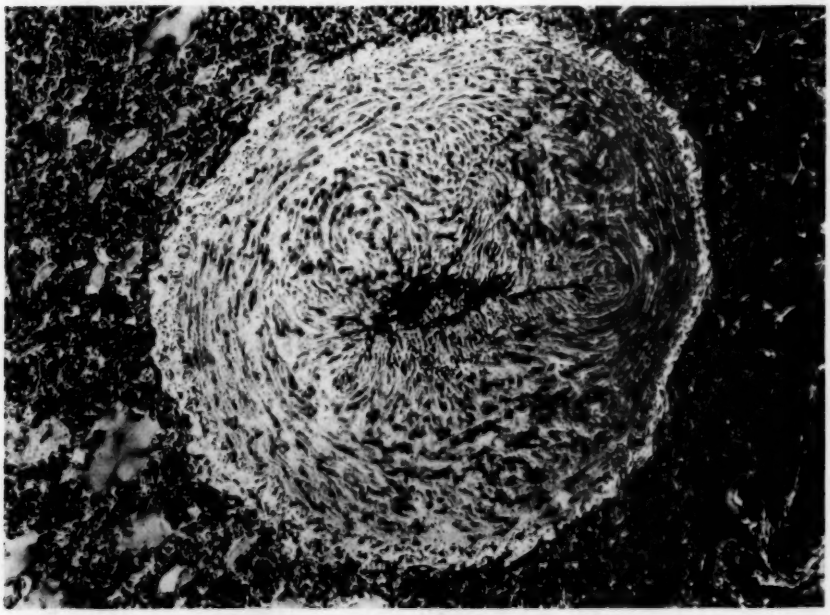


Fig. 5.—Muscular artery of rabbit. Note the fat in the lumen of the vessel and the absence of fat in the intima (dark-staining substance). (Sudan III; × 75.)

serum (fig. 6*A*). It seemed that after the internal elastic membrane had been destroyed, the infiltration of lipoids with the serum was unchecked and the expression of the same fruitless, accounting for the overwhelming diffuse deposit found there (fig. 6*B*).

As one approached the arterioles, where the internal elastic membrane disappeared, lipoid deposit was again occasionally evident in the intima (liver, spleen, kidney, etc.).

From a physical standpoint the infiltration of cholesterol in the aorta is dependent on the cholesterol content of the serum, the blood pressure and the nature of the elastic membranes. In the rabbit's aorta, where

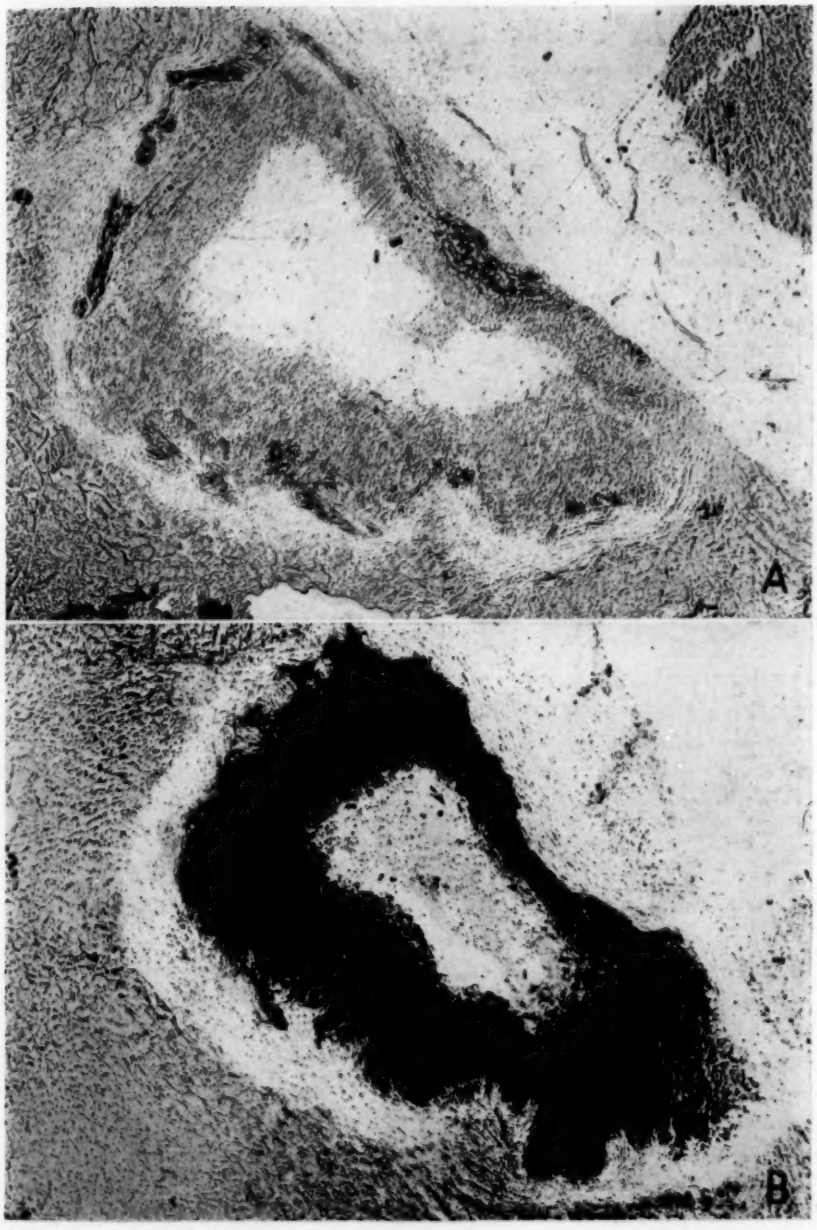


Fig. 6.—*A*, muscular artery of a rabbit showing fragments of the internal elastic membrane (dark-staining fibers). (Weigert's elastica stain; × 75.) *B*, same artery showing marked fat deposit in the intima and the media (dark-staining substance). (Sudan III; × 75.)

no definite elastic limiting membranes are present, the lipoid-containing serum during systole is pressed into the wall beneath the endothelium and between the elastic fibers. When cholesterol is present in increased quantities in the serum it may be deposited there. In the peripheral vessels the lipoids are arrested at the well developed internal elastic membranes.

The expression of the cholesterol-containing serum that occurs with the diastolic recoil of the vessel is dependent on the structure of the elastic limiting membranes, the latter's distance from the lumen of the vessel, and the irregularity of the contracting parts. In the aorta of the

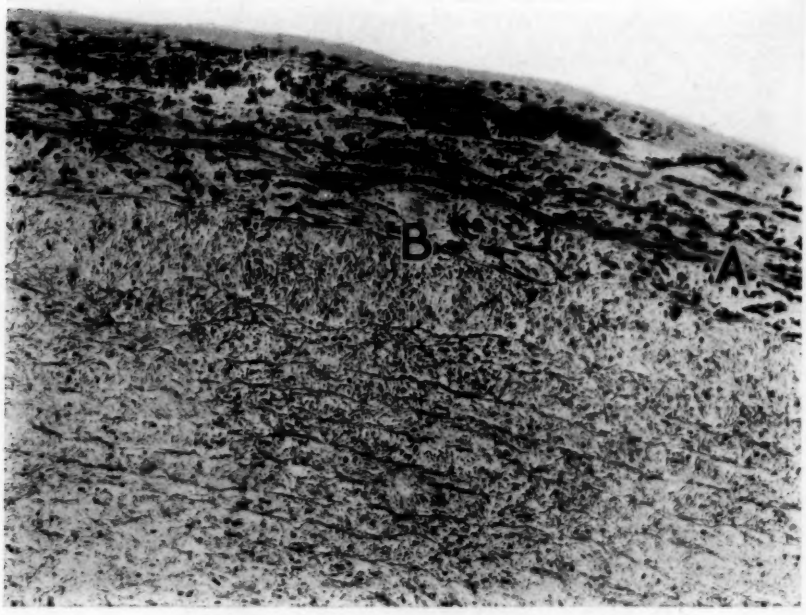


Fig. 7.—Early fat deposit in the abdominal portion of the aorta (dark-staining substance). Note that the lipoid substance is at some distance from the external limiting membrane (*A*). The internal elastic membrane is insignificant (*B*). (Sudan III; × 100.)

rabbit the expression of the lipoids was incomplete, because the contraction of the vessel was uniform (the elastic and muscle fibers are connected and dependent on one another—Benninghoff), and because the loosely arranged elastic fibers acted as a barrier to the expression as well as to the infiltration. In the peripheral vessels the irregularity of the contracting parts (the well developed elastic membrane contracts more forcibly than the remaining parts) and the absence of elastic barriers between it and the lumen effected a complete expression and may account for the absence of lipoids in the intima. It seemed strongly

suggested then that the deposit of lipoids in an artery was dependent not only on the infiltration of cholesterol but also on the expression of the same.

How can this mechanism be applied to the human being? The fibro-elastic layer of the intima of the aorta is markedly developed in the abdominal portion (fig. 3 *B*). In the thoracic portion this layer is characterized by a narrow dense fibro-elastic membrane (fig. 3 *A*). Correspondingly, the distance between the lumen of the aorta and the external limiting membrane of this layer increases from the thoracic to the abdominal portions. The internal elastic membrane is poorly developed throughout, while in the peripheral vessels it is markedly developed (Benninghoff, Nordmeyer).

With systole the lipoid-containing serum infiltrates into the entire arterial tree (Ribbert, Aschoff,[c, f] Hueck), and the lipoids may be arrested at the elastic barriers. The expression of the same will vary, depending on the factors mentioned.

In the thoracic portion the expression of lipoids will be more effective than in the abdominal portion of the aorta, because in the former the distance between the limiting membranes and the lumen is smaller. Also this membrane is denser and offers a more effective limitation to the infiltration as well as a more efficient expulsion. The fibro-elastic layer of the abdominal portion of the aorta corresponds somewhat to that of the rabbit's aorta in that a broad layer of loosely arranged elastic fibers is present between the lumen and the limiting membranes. Here the infiltration of lipoids extends among the loosely arranged elastic fibers and an effective barrier is reached only at some distance from the lumen. With diastole the loosely arranged fibers between the lumen and the external limiting membranes form a similar barrier to the outflowing substance (fig. 7). This dissimilarity of structure may account for the greater frequency of atherosclerosis in the abdominal as compared with the thoracic portion of the aorta.

In the peripheral muscular vessels, where the internal elastic membrane is in proportion much better developed than in the aorta, with the diastolic recoil this membrane contracts forcibly and out of proportion to the other parts (the elastic fibers and the muscle fibers are two distinct systems in the muscular arteries—Benninghoff), thus effecting a more thorough expression. One has but to note the difference in the furrowing of the internal elastic membrane of muscular arteries in histologic preparations and to compare it with that of the aorta to be convinced of the inequality of contraction of the various layers of an artery.

In the arterioles, where the internal elastic membrane is practically absent, a deposit of lipoid and hyalin was noted in human beings, especially when hypertension was present (Gull and Sutton, Volhard, Rühl).

Now the question arises: Why is the lipoid deposit found to only a slight extent in persons up to 25 years of age, being even then reversible, while in older persons the fatty deposit increases rapidly and is non-reversible (Aschoff[d])? This question is asked in the light of the fact that the histologic structure of the aorta under 25 years is not much different from that over this age.

In young as in old persons the mechanism of infiltration is probably not much different.

In nursing infants, in young persons at puberty, in women during pregnancy, and in persons who have passed through certain infectious diseases (especially typhoid fever—Ophüls), owing to a relative increase in the blood cholesterol or a disturbance of its mechanism, a deposit of cholesterol often occurs in the aorta, as the equilibrium between infiltration and expression is disturbed. With the recession of the cholesterol disturbance lipoids disappear from the aorta as a result of the compensated expression and the activity of the histiocytes (Langhans' cells) and because the fat is not "bound" to the interstitial substance or the elastic lamellae. With age two additional factors enter: (1) the aging of colloids which may bind or precipitate the fat (Bürger, Thannhauser, Wells, Aschoff[d]) and (2) the stretching or the disappearance of the elastic fibers preventing complete expression.

But not all people age at a similar rate and, as has been shown experimentally, the endowment of the elastic tissue may vary with different persons as well as in a given subject. Finally, with changes of the colloid and decreased elasticity of the vessels an atherosclerosis does not necessarily follow, as will be shown later. True enough, a senile arteriosclerosis may develop with age with even a slight fat deposit due to degenerative changes, but this emphatically is not atherosclerosis, and the latter is the more prevalent and more dreaded occurrence.

How is one going to determine the degree of aging in a vessel? From a histologic standpoint this is practically impossible in the early stages, as there is no method of determining the aging of colloid histochemically. Incubating aortas with sodium hydroxide (up to 20 per cent) or acetic acid (from 5 to 20 per cent) until a definite softening has taken place grossly does not show any alterations microscopically (Camac).

It is generally agreed that stretching of the elastic membranes and their replacement by fibrous tissue with age cause a dilatation of the vessel, and this process supposedly begins after the ascending stage of life (33 years, Jores, E. Kaufmann, Rössle, Aschoff,[c] Wells, Benninghoff, Bramwell, Duguid). As in the early stages of this process no microscopic changes are found, one has only the size of the vessel to rely on. In a large group of cases some insight into the degree of aging might be had by this method of comparison. It is admitted that this is a crude procedure, but one has none better at hand.

Table 23 presents the three measurements of the aorta for the average groups of males and females of both races. A progressive increase with age was noted for all cases (Jaffé and Sternberg, Rössle, L. Kaufmann, Suter). For the white race the highest percentage of dilatation was found at the level of the diaphragm (58 and 65 per cent in males and females, respectively). The greatest dilatation for the colored race was found at the bifurcation of the aorta (60 and 69 per cent, respectively). Some degree of error in the third measurement may be present, for when calcification occurs, the vessel may become pipestem-like and narrow. As this is not a frequent occurrence and was present in both white and colored races with equal frequency, the possibility of error is not great, considering the number of cases examined.

For the average group, embracing all factors that may involve the aorta (age, blood pressure, cholesterol metabolism, etc.), there was on

TABLE 23.—*The Measurements of the Aorta of the White and Colored Races from 25 Years Onward*

	White								Colored							
	Male				Female				Male				Female			
		Measurements, Mm.				Measurements, Mm.				Measurements, Mm.				Measurements, Mm.		
Age	Cases	1st	2nd	3rd	Cases	1st	2nd	3rd	Cases	1st	2nd	3rd	Cases	1st	2nd	3rd
25–30	5	57	39	32	10	53	34	29	8	62	40	30	19	57	39	29
31–40	24	65	46	37	20	59	39	30	26	66	45	33	16	63	43	33
41–50	52	72	49	39	29	66	47	35	21	68	46	40	15	67	50	38
51–60	52	75	53	42	21	66	47	37	15	75	54	45	10	76	52	37
61–70	40	78	57	44	17	75	54	40	8	76	55	47	4	79	60	49
71–	25	82	60	42	13	75	56	40	5	76	59	48				
% increase		52	58	40		42	65	39		23	48	60		37	54	69

the average a 50 per cent increase in the size of the vessel throughout. Since physiologic growth is practically complete at the end of the ascending stage of life, this dilatation must be ascribed mainly to a degenerative process (Aschoff [d, e, f]).

If age were the only factor involved in the production of atherosclerosis, one would expect that aortas showing similar changes of age (as denoted by dilatation) should contain a similar amount of fat. That this is not the case is seen in table 24 A, B and C, where the measurements of the aorta are given according to the severity of the atherosclerosis, and in which cases are noted in which marked dilatation of the aorta occurred without atherosclerosis (table 24 A). True that the number of such cases decreases with age, and table 25 shows that there are no smooth aortas after 70 years, but it is significant that there are many present at 60 years (up to 27 per cent) and that they may be found even between 61 and 70 years. On the contrary, severe atherosclerosis occurred in persons in whom comparatively little dilatation of the vessels had occurred.

If it were possible to conceive that the other factors influencing atherosclerosis, such as a disturbance in the cholesterol metabolism and an increased blood pressure, could be staved off, the number of smooth aortas, irrespective of their aging, would probably be greatly increased.

It would be of great importance if in a similar way the degree of aging could be ascertained in various diseases, but here the other influencing factors are such that they may determine the size of the dilata-

TABLE 24.—A. *The Width of the Ascending Aorta in Various Conditions*

	White												Colored											
	Male						Female						Male						Female					
Age	S	SM	MS	AA	EH	sH	S	SM	MS	AA	EH	sH	S	SM	MS	AA	EH	sH	S	SM	MS	AA	EH	sH
A. The Width Above the Aortic Cusps																								
25–30	57				60	55	53					53	60			68	60	60	56	60		60		60
31–40	64	68	68	68	67	71	58	65		68	74	65	64	68	69	69	70	65	60	66	65	66	64	62
41–50	73	72	70	72	71	73	63	65	69	67	65	69	65	74	69	75	68	75	62	72	68	67	69	67
51–60	71	75	77	76	79	77	66	67	65	66	63	67	68	77	76	77	86	72	76	73	79	76	82	76
61–70	83	77	79	78	78	77		74	76	75	70	74	78	73	76	75	75	75						
71–		80	83	80	81	81		76	73	74	77	71		87	69	76	72	77		71	89	79	89	
B. The Width at the Diaphragm																								
25–30	39				42	38	34					34	41			37	37	41	38	42		42		42
31–40	45	47	51	49	49	50	39	40		43	50	40	42	44	53	47	49	45	41	48	45	48	49	43
41–50	49	49	52	49	49	49	44	46	51	48	50	48	49	49	45	48	47	47	46	51	54	53	55	47
51–60	49	52	53	54	56	54	46	48	51	48	48	47	52	50	63	52	57	49	48	52	53	53	50	53
61–70	53	57	56	57	60	56		52	56	54	52	53	55	58	63	57	60	55						
71–		58	62	60	62	59		54	58	57	60	56		68	56	59	62	61		56	67	60	67	
C. The Width at the Bifurcation																								
25–30	32				36	31	29					29	31			28	28	31	28	30		30		30
31–40	36	36	40	39	40	38	31	32		34	39	32	33	37	40	38	40	35	31	36	40	37	36	35
41–50	38	36	42	40	39	38	35	37	39	37	37	40	40	38	40	39	40	37	35	38	40	39	42	36
51–60	39	43	43	43	43	44	36	37	43	38	37	37	40	41	54	42	37	38	36	38	38	38	40	38
61–70	43	44	44	44	49	41		38	42	40	44	41	49	41	54	48	48	40						
71–		47	47	46	45	49		38	41	40	42	41		55	47	50	60	49		48	50	49	50	

S = smooth.
SM = slight to moderate atherosclerosis.
MS = moderate to severe atherosclerosis.
AA = all cases of atherosclerosis.
EH = essential hypertension.
sH = without hypertension.

tion of the aorta and the measurements would be misleading unless carried out in a very large group. It is sufficient to say that in the supposedly degenerative diseases (diabetes mellitus, carcinoma, tuberculosis) there was no greater dilatation of the aorta, or aging, than was found in the average (also L. Kaufmann). Surprisingly, with essential hypertension, when sufficient cases were available (table 24 A, B and C), the width of the aortas was only slightly over that of the smooth aortas (Jaffé and Sternberg) and in many instances was equal to it (Kani). When the cases of atherosclerosis with hypertension and without hypertension were compared (table 24 A, B and C) the width was usually slightly increased in favor of the former (also Scheel, Jaffé and Sternberg) but not always so.

Figure 8 illustrates what has already been said. In this graph the widths of smooth aortas, those showing moderate to severe atherosclerosis and those in cases of hypertension in the white males were plotted, as this group comprised the greatest number of cases and represented the average trend of all groups.

Under the first measurement of the aorta, the width of the smooth ones excelled that of aortas presenting moderate to severe atherosclerosis

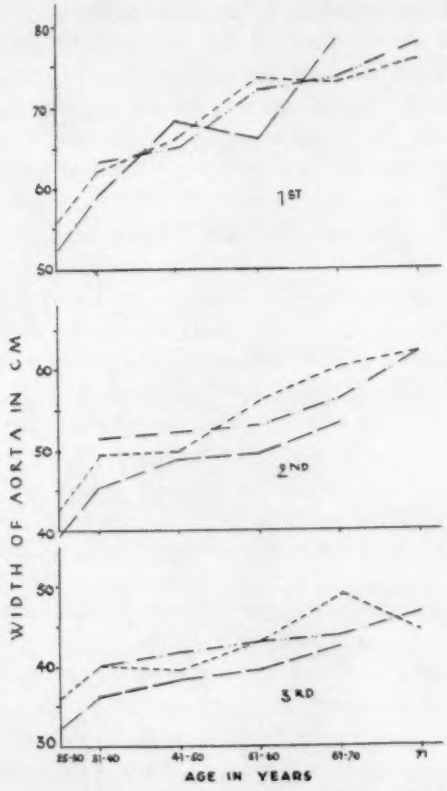


Fig. 8.—Measurements of the aorta in various conditions in different age groups of white males. Smooth aortas (— —); aortas showing moderate to severe atherosis (— .. —) aortas from persons with essential hypertension (- - - -).

and that of aortas of persons with hypertension, between 41 and 50 years and 61 and 70 years. Indeed, at from 61 to 70 years the width of the smooth aorta was greater than that of the atherosclerotic aorta at 71 years and over.

With the next two measurements, the width of the aorta ran somewhat parallel to the severity of atherosclerosis, but as atherosclerosis

is most prevalent in the abdominal portion of the aorta, other factors than age came into consideration. In the ascending portion of the aorta, where atherosclerosis is uncommon in all cases, a more uniform basis of comparison is available, and supposedly only the changes of age are there represented.

Summary.—From a histologic study of the arteries of the cholesterol-fed rabbit and the human being it is suggested that not only the infiltration of lipoids influences the latter's deposit in the arteries but that the expression of the lipoids is of equal importance.

The degree of development of the elastic limiting membranes influences both the infiltration and the expression. From a physical standpoint the latter is dependent on the nature of the elastic membranes,

TABLE 25.—*The Percentage of Cases With and Without Atherosclerosis According to Age, Sex and Race*

	White								Colored							
	Male				Female				Male				Female			
Age	Cases	No. cA	% cA	% sA	Cases	No. cA	% cA	% sA	Cases	No. cA	% cA	% sA	Cases	No. cA	% cA	% sA
25-30	5	0	0.0	100.0	10	0	0.0	100.0	9	2	22.2	77.8	18	4	22.2	77.8
31-40	24	9	37.5	62.5	20	3	15.0	85.0	26	11	42.2	57.8	16	7	43.7	56.3
41-50	52	26	50.0	50.0	29	19	65.6	34.4	21	7	41.6	58.4	15	11	73.3	26.7
51-60	52	38	73.0	27.0	19	12	63.1	36.9	15	11	78.9	21.1	10	8	80.0	20.0
61-70	40	37	92.5	7.5	17	17	100.0	0.0	8	6	75.0	25.0	2	1	50.0	50.0
71-	25	25	100.0	0.0	13	13	100.0	0.0	5	5	100.0	0.0	2	2	100.0	0.0

No. cA = number of cases with atherosclerosis.
% cA = percentage of cases with atherosclerosis.
% sA = percentage of cases without atherosclerosis.

the distance between the limiting membrane and the lumen of the vessel, and the inequality of the contraction of the various parts.

To demonstrate the foregoing statements, the following evidence was given: In the muscular type of arteries in the rabbit as in man, where the internal elastic membrane is well developed, there was from little to no lipoid deposit in the intima. In one muscular artery, where the internal elastic membrane had given way, a marked diffuse lipoid deposit occurred. When a moderate amount of lipoid was deposited among the elastic fibers of the rabbit's aorta it was situated, to a great extent, on the distal and not on the proximal aspect of the fiber. In the arterioles, where the internal elastic membrane is poorly developed or absent (spleen, kidney, liver), a lipoid deposit was again occasionally noted.

In the human being the development of the fibro-elastic layer of the abdominal portion of the aorta is marked, while in the ascending portion it is comparatively slight. This is considered to be the result

of a physiologic process in the ascending stage of life dependent on the greater circulatory demands made on the abdominal portion of the aorta.

A comparative study of the measurements of the aorta from birth to 30 years for the white and colored races revealed that there was no difference in the widths of the aortas for all cases up to 11 years. From then on the female aorta did not progress as rapidly as the male, especially the abdominal portion. The latter observation was explained by the difference in physical activity of the sexes after 11 years or thereabouts.

The abdominal portion of the aorta for both sexes and races increased in width to a higher degree (25 per cent) than the ascending portion. This difference is offered as an explanation of the variation in the development of the intima.

The fibro-elastic layer of the abdominal portion of the aorta, because of its marked development and its loosely arranged elastic fibers, serves as a barrier for the infiltration as well as for the expression of lipoid substances. This fact may probably account for the greater incidence and severity of atherosclerosis there.

The infrequency of lipoid deposition in the intima of the muscular arteries is explained by its strongly developed internal elastic membrane, which effects a more thorough expression of infiltrating substances. The poorly developed elastic membranes of the arterioles may account for their predisposition to hyaline and lipoid deposit.

In the ascending stage of life, when a disturbance of the lipoid metabolism takes place, as demonstrated by a relative increase of the blood cholesterol, the equilibrium between infiltration and expression is disturbed in favor of the former. When the hypercholesteremia subsides, the expression component becomes compensated for and the cholesterol disappears from the aorta.

In adult persons, and more particularly in the descending stage of life, the aging of the colloids as well as the decreased elasticity of the vessel favors a binding or precipitation of the lipoids as well as a decreased expression of the same with the resultant irreversible cholesterol deposit.

Judging the aging of an aorta by the degree of dilatation, it was found that aging is a factor of first importance in the development of atherosclerosis. Aging in itself, however, does not lead to an atherosclerosis but to a pure senile sclerosis. The latter's occurrence is much less frequent than the former's.

Aortas in degenerative diseases, such as diabetes mellitus, tuberculosis and carcinoma, did not show any greater degree of dilatation than was found in smooth aortas. In essential hypertension the degree of dilatation was somewhat higher than that found in cases without hypertension.

B. THE BEARING OF HYPERTENSION ON THE INCLINATION TO ATHEROSCLEROSIS (F.A.A)

That arterial tension influences the development of atherosclerosis is a long established fact (Jores, Aschoff,[e, b] Marchand, E. Kaufmann). Pointed examples are seen in the high incidence of changes in the pulmonary artery following increased pulmonary tension or in congenital stenosis of the aorta (Sternberg, Moschcowitz, Rosenthal). Whether the increased tension hastens the aging of the vessel or whether it favors the infiltration of cholesterol will be discussed later.

Experimentally, the development of atherosclerosis in cholesterol-fed animals is hastened by the addition to the diet of a substance elevating the blood pressure, such as epinephrine (Anitschkow,[c] Schmidtmann, Pfleidner). Increased blood pressure alone will not lead to a true athero-

TABLE 26.—*The Heart and Body Weights in All Cases Examined*

	White						Colored					
	Male			Female			Male			Female		
Age	Cases	Heart Wt., Gm.	Body Wt., Lbs.	Cases	Heart Wt., Gm.	Body Wt., Lbs.	Cases	Heart Wt., Gm.	Body Wt., Lbs.	Cases	Heart Wt., Gm.	Body Wt., Lbs.
25–30	5	276	114	10	284	117	8	327	112	10	278	119
31–40	24	395	128	20	282	119	26	385	132	16	404	120
41–50	52	396	129	29	342	119	21	373	132	15	453	129
51–60	52	379	126	21	335	105	15	361	131	10	359	125
61–70	40	372	119	17	374	122	8	434	135	4	355	146
71–	25	416	140	13	340	112	5	419	132			

sclerosis of the aorta in rabbits (Rühl,[b] Nuzum, Seegal, Garland and Osborne, Anitschkow [c]).

That atherosclerosis of the aorta is always accompanied by hypertension (Moschcowitz,[a, b]) is open to question (Hasenfeld, Hirsch, Lange [b, c]).

As a rule the weight of a heart and the blood pressure run parallel (Aschoff,[e] Lange,[b, c] Gewert). For the material presented it was found that a hypertrophy of the heart and thus hypertension could be considered when the heart weight was 400 Gm. or over for the male, and 375 Gm. or over for the female (excluding diseases of the heart proper). This weight was taken with all the blood removed and about from 1 to 3 cm. of the aorta attached. Naturally, lower values are obtained if the heart is prepared after the method of W. Müller, as was carried out by Rössle, Lange and also Levine and Carr, working in this laboratory. For a large material the method here employed carries but a small percentage of error (Gewert).

In figure 9 and table 26 the heart weights are given according to age, sex and race. For all cases the heart weight increased until the age from 40 to 50 and then became inconstant (also Fahr,[b] Müller, Rössle,

L. Kaufmann, Gewert). Although the body weight increased along with the heart weight for a general group, the relative heart weights also increased with age (Müller, Fahr, Rössle). As the present study was concerned only with the blood pressure as determined by the heart weight, the relative heart weights are not recorded (cf. Levine).

In comparing the heart weights with the fat angles of the aorta (F.A.A.) there was a certain amount of paralleling which suggested an influence of increased arterial tension (part I C).

In dividing the cases according to the severity of the atherosclerosis (table 27 A, B and C) it was noted that the weight of the heart increased

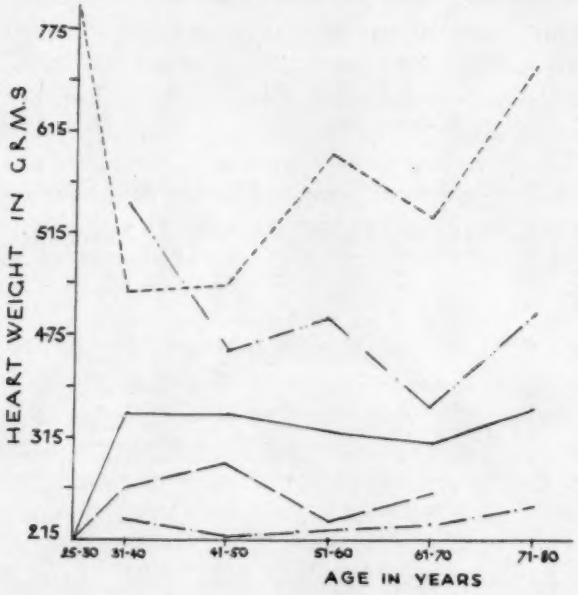


Fig. 9.—Heart weights corresponding to aortas in various conditions in different age groups of white males: average (——); smooth aortas (— —); aortas showing moderate to severe atherosclerosis (— . . —); aortas from persons with essential hypertension (- - - -); aortas from persons with carcinoma (—.—.)

with the severity of the atherosclerosis. However, when the groups were considered individually and the heart weight compared with the F.A.A. (part I B), such a parallelism was not so striking.

To have a larger number of cases for comparison, all cases of atherosclerosis were grouped together (table 28). Here one found that although the F.A.A. was about equal for all groups, the heart weights were decidedly different. Thus the heart weights from 25 to 50 years were usually greater than those past 50 years but the inclination to atherosclerosis was similar. Increased blood pressure, as determined

by the size of the heart, and the intensity of atherosclerosis are thus not directly proportional.

Under smooth aortas the heart increased in weight until 50 years (in the white female up to 60 years). From there on the heart became

TABLE 27.—*The Heart and Body Weights Corresponding to the Three Groups of Aortas*

	White						Colored					
	Male			Female			Male			Female		
Age	Cases	Heart Wt., Gm.	Body Wt., Lbs.	Cases	Heart Wt., Gm.	Body Wt., Lbs.	Cases	Heart Wt., Gm.	Body Wt., Lbs.	Cases	Heart Wt., Gm.	Body Wt., Lbs.
A. Smooth Aortas												
25–30	5	276	114	10	284	112	7	315	116	14	261	116
31–40	15	324	124	17	269	118	15	353	130	9	270	106
41–50	26	349	125	10	243	109	14	352	129	4	307	147
51–60	14	285	114	7	329	158	4	333	161	2	270	109
61–70	3	320	117				2	375	123			
71–												
B. Aortas Showing Slight to Moderate Atherosclerosis												
25–30										4	266	130
31–40	6	476	129	2	235	101	8	400	139	6	383	119
41–50	20	437	131	14	318	135	11	368	126			
51–60	26	392	135	40	311	109	10	385	116	5	380	120
61–70	20	357	112	9	339	117	4	402	128			
71–	11	310	117	5	370	136	2	402	119			
C. Aortas Showing Moderate to Severe Atherosclerosis												
25–30							1	325	86			
31–40	3	600	146	1	640	112	3	503	109	1	320	128
41–50	6	461	149	5	552	136	2	465	147	8	538	128
51–60	12	494	136	4	433	103	1	230	158	3	413	148
61–70	17	404	126	8	418	118	2	460	111			
71–	14	492	153	8	322	118	3	460	141	2	405	162

TABLE 28.—*The Relationship of the Heart Weight and the F.A.A. in All Cases of Atherosclerosis*

	White								Colored							
	Male				Female				Male				Female			
Age	Cases	Fat, Gm.	F.A.A., Degrees	Heart Wt., Gm.	Cases	Fat, Gm.	F.A.A., Degrees	Heart Wt., Gm.	Cases	Fat, Gm.	F.A.A., Degrees	Heart, Wt., Gm.	Cases	Fat, Gm.	F.A.A., Degrees	Heart Wt., Gm.
25–30												362	5	0.280	63.8	366
31–40	9	0.363	59.8	517	3	0.332	57.5	370	11	0.339	57.8	429	7	0.388	61.5	374
41–50	26	0.563	61.2	442	19	0.484	57.2	427	10	0.474	56.5	374	11	0.702	66.3	518
51–60	38	0.643	57.3	421	14	0.736	60.8	324	16	0.550	53.0	371	8	0.619	56.2	382
61–70	37	0.856	59.0	377	17	0.893	60.2	374	6	1.207	67.2	455				
71–	25	1.086	60.5	424	13	1.189	62.9	353	5	1.289	64.8	437	3	1.299	66.8	355

smaller (Fahr, Rössle, L. Kaufmann; the Gewert normal values decreased in size after 40 years). The females of both races had smaller hearts than the corresponding males. The normal heart weight of the colored male was somewhat greater than that of the white male.

More positive evidence demonstrating the influence of hypertension on atherosclerosis is seen in table 29, in which only the cases of essential hypertension are included. The inclination to atherosclerosis lay between 60° and 65°, which was interpreted as a moderate to severe involvement of the aorta. For every age group, this inclination was greater than for the average group.

Similarly, chronic glomerular nephritis, because it was usually accompanied by an increased arterial tension, had also a higher incidence of atherosclerosis (cf. part II). As the degree of hypertension in nephritis was usually much lower than that of essential hypertension, the F.A.A. was correspondingly smaller. The small number of cases prevented the construction of a table, but the heart weights were as much as 30 per cent higher for this group than for the average.

Thus far the interconnection between atherosclerosis and hypertension has been stressed. In table 30, the cases of atherosclerosis without hypertension are listed. The heart weights were about similar to those with the smooth aortas and in some instances were smaller. An evaluation of the incidence of atherosclerosis without hypertension (table 30) proved that somewhat less than half the cases were not associated with an increased arterial tension.

By reversing the percentage of the cases without atherosclerosis in table 30, the incidence of hypertension with atherosclerosis could be deducted. In the white male hypertension played its greatest rôle up to 60 years, whereas in the white female the factor was most prominent after 60 years (effects of the climacteric). For the colored male there was a more or less equal distribution with age, while for the colored female hypertension was most marked between 41 and 50 years.

Drawing their conclusions from sources similar to those of the foregoing observations Jaffé [b] and Shapiro reported that the incidence of malignant nephrosclerosis was about five times as frequent in the colored race as in the white. The colored female was the most susceptible. The data given by Jaffé are as follows: 0.92 and 1.3 per cent for the male and female, respectively, of the white race, and 5 and 7.9 per cent for the colored male and female, respectively. The average age of colored persons with hypertension was 42 years. Hypertension in general was more prevalent in the colored than in the white race.

The foregoing evidence testifies to the importance of hypertension in the augmentation of atherosclerosis, but it shows equally that atherosclerosis can occur without hypertension (also Lange, Hasenfeld, Hirsch).

A slight diversion is here in order to examine the bearing of obesity on atherosclerosis and also on hypertension. There is no proof that overnutrition or undernutrition leads to atherosclerosis (Weiss and

TABLE 29.—*The Relationship of the Heart and Body Weights to the F.A.A. in Hypertension*

Age	White										Colored									
	Male					Female					Male					Female				
	Fat, Gm.	F.A.A., Degrees	Av. F.A.A., Degrees	Heart Wt., Gm.	Body Wt., Lbs.	Fat, Gm.	F.A.A., Degrees	Av. F.A.A., Degrees	Heart Wt., Gm.	Body Wt., Lbs.	Fat, Gm.	F.A.A., Degrees	Av. F.A.A., Degrees	Heart Wt., Gm.	Body Wt., Lbs.	Fat, Gm.	F.A.A., Degrees	Av. F.A.A., Degrees	Heart Wt., Gm.	Body Wt., Lbs.
25-30.....	0.140	43.9	22.9	760	139 (1)*	.....	....	....	...	.....	0.577	77.0	38.6	328	88 (1)	0.538	76.4	44.3	560	140 (1)
31-40.....	0.512	67.5	39.8	512	130 (2)	0.659	72.6	25.9	640	112 (1)	0.460	65.0	44.2	546	127 (6)	0.288	53.4	47.4	460	104 (2)
41-50.....	0.365	49.0	48.5	533	137 (8)	0.503	62.4	49.0	502	125 (7)	0.602	62.9	39.5	533	134 (3)	0.729	67.2	60.4	603	110 (8)
51-60.....	1.111	69.9	50.8	649	141 (6)	1.00	67.9	52.8	433	111 (3)	0.642	57.4	48.2	423	88 (4)	0.718	60.0	50.8	570	135 (1)
61-70.....	0.924	61.2	57.6	584	132 (5)	0.487	43.2	60.2	510	217 (1)	1.233	67.6	61.8	523	162 (4)	.....	....	....	...	.....
71-	1.673	70.0	60.5	735	138 (3)	0.863	54.8	62.9	375	129 (5)	0.981	58.0	64.8	560	145 (1)	1.609	69.3	61.4	405	161 (2)
Average.....		60.2	46.7				60.2	50.1				64.7	49.5				65.2	52.8		

* Figures in parentheses is the number of cases.

Minot), but it is generally conceded that obesity and hypertension exist together (Joslin, Dunham, Hunter and Rogers, O'Hara, Herrich, cited by Wyckoff).

In table 27 A, B and C, in which the body weights are given according to the severity of the atherosclerosis, there is no striking difference in the body weights of these groups. Thus the relative heart weights would necessarily be higher in the severer cases of atherosclerosis (also Gewert).

In the hypertension groups the body weights as a whole are greater than they are in the average groups (tables 29 and 26, respectively), but they cannot be considered as obese. It must be borne in mind that the cases examined were drawn from a poor class of people. When sufficient cases were available, the body weight on the average was

TABLE 30.—*The Relationship of the Heart and Body Weights in Cases of Atherosclerosis Without Hypertension*

	White									Colored								
	Male					Female				Male					Female			
	Cases					Cases				Cases					Cases			
		Without Hypertension					Without Hypertension				Without Hypertension					Without Hypertension		
Age	Atherosclerosis	No.	%	Heart Wt., Gm.	Body Wt., Lbs.	Atherosclerosis	No.	%	Heart Wt., Gm.	Body Wt., Lbs.	Atherosclerosis	No.	%	Heart Wt., Gm.	Body Wt., Lbs.	Atherosclerosis	No.	%	Heart Wt., Gm.	Body Wt., Lbs.
25–30																				
31–40	9	1	11.1	350	121	3	2	66.6	235	101	11	5	46.4	295	127	7	3	42.8	278	126
41–50	26	11	42.3	297	112	19	8	42.1	251	126	7	4	57.1	277	140	11	2	18.1	315	96
51–60	38	17	44.6	297	120	12	9	75.0	291	104	11	6	54.6	321	126	8	5	62.5	298	121
61–70	37	22	59.4	313	111	17	8	47.0	230	111	6	2	33.3	295	96					
71–	25	14	56.0	329	125	13	4	30.7	284	113	5	2	40.0	355	114					
			48.1					48.4					47.5					36.1		

below 140 pounds (63.5 Kg.). The lowest value was 88 (39.9 Kg.) and the highest 217 pounds (98.4 Kg.). The relative heart weights in the groups with essential hypertension are higher than in any other group (Levine and Carr, Gewert).

Compared with clinical observations, the blood pressure in an average group of white persons of the Western Hemisphere increases with age up to about 60 years (Romberg,[a, b] Volhard, Gager, Blackford, Bowers and Baker, Donnison, and others). However, what is considered as the average increase for the white civilized race is not the average for other races. The maximum normal blood pressure at 60 years was placed at 160 systolic and 100 diastolic by Romberg. For the colored people of eastern Africa it is 105 systolic and 67 diastolic (Donnison); for the Eskimos it is 129 systolic and 76 diastolic (Thomas). Low values were also reported for the Indians (Bengal) by Rogers, for the Chinese by Tung and Foster, for the Japanese by Rubner (quoted by Raab), and for the Mohammedans by Ruffer and Ismail.

Within the folds of the white race, the so-called normal blood pressure may in reality be abnormal. Saile has clearly shown that monks who live under different environments and diets have marked variations in their blood pressure. In one group who were strict vegetarians and spoke little the average blood pressure rarely went over 120 mm. of mercury (24 per cent), while in other monks who lived on an average diet, going among their parishioners, the blood pressure was practically always over 120 (70 per cent). The "normal" blood pressure of the white race in late adult life more likely borders on hypertension and may partly account for the high incidence of aortic changes.

It does not follow that a lower blood pressure excludes the possibility of atherosclerosis. As has been shown, in 48 per cent of these cases no inclination to an increased arterial tension was found. The Indians examined by Rogers and the Mohammedans examined by Ruffer have a lower blood pressure than the white race and supposedly a similar incidence of atherosclerosis. This would be compatible but it does not disprove the importance of hypertension.

Similar analogies can be found in studying the various diseases, considering as before that the "average" tables embrace equally the average possibilities that may lead to atherosclerosis.

In acute infectious diseases the cholesterol metabolism was considered as not appreciably altered. For the white race the F.A.A.s were everywhere similar except between 25 and 30 years. In comparing the respective heart weights (table 31) it is evident that for this group the weight was much lower than for the average group. Similarly, for the colored race differences were found which could be explained on the basis of the blood pressure (heart weights).

On the contrary, in carcinoma in which the heart weights were much lower than the average (also Gewert), the F.A.A.s were usually either equal to or slightly less than the average. Notwithstanding the fact that the heart weights were lower than those for the hearts with smooth aortas (F.A.A., 19.3°), the average F.A.A. for carcinoma was 43.1° (table 32). Increased blood pressure was certainly not an outstanding feature in this series.

In tuberculosis a relationship similar to that in carcinoma was found. Because of the lack of a sufficient number of cases a table was not made. The heart weights were as much as 25 per cent lower than for the average group. Other factors that increase blood pressure must be at work to effect the atherosclerosis.

With diabetes the F.A.A. was 59.7° or about 20 per cent greater than the average (48.8°). The heart weights for diabetes were as a rule about 20 per cent less than for the average. Here again the arterial tension played a minor rôle.

TABLE 31.—*The Relationship of Acute Infectious Diseases to the Heart Weight and the F.A.A.*

	White								Colored							
	Male			Female					Male			Female				
Age	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	F. A. A., M. & F., Degrees	Av. F. A. A., Degrees	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	F. A. A., M. & F. Degrees	Av. F. A. A., Degrees
25-30	2	212	276	2	252	284	12.0	19.6	1	340	327	6	269	278	24.3	43.0
31-40	6	382	395	10	257	282	39.6	34.0	4	331	385			403	46.2	44.2
41-50	9	407	396	4	262	342	46.3	48.4	7	353	373	3	339	452	28.4	46.0
51-60	5	417	379	3	280	335	45.2	51.2	8	351	361			359	41.4	48.2
61-70	6	331	372	3	488	337	46.8	58.4	2	375	434	1	425	355	56.9	62.0
71-	5	407	416	1	380	340	57.8	61.4								

TABLE 32.—*The Relationship of Carcinoma to the Heart Weight and the F.A.A.*

	White								Colored							
	Male			Female					Male			Female				
Age	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	P. A. A., M. & F., Degrees	Av. F. A. A., Degrees	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	Cases	Heart Wt., Gm.	Av. Heart Wt., Gm.	F. A. A., M. & F. Degrees	Av. F. A. A., Degrees
25-30										320	327	1	190	278	49.5	40.7
31-40	5	292.0	395	2	230	282	31.0	34.0	2	195	403	1	195	403	17.0	45.0
41-50	10	267.5	396	7	248	342	38.5	48.4	4	295	373	1	330	452	40.2	44.0
51-60	16	383.0	379	6	270	335	37.3	51.0	1	270	361	2	315	359	31.3	49.7
61-70	11	286.0	372	3	285	373	57.5	58.4						Average.....	34.5	45.1
71-	4	304.0	416	3	235	340	51.3	61.4	1	355	419					
					Average.....		43.1	50.1								

M & F = male and female.

Summary.—Increased arterial tension plays an important rôle in the development of atherosclerosis, and when the former is present, the latter will invariably follow. Hypertension without atherosclerosis can occur—in the cases studied, to the extent of 7 per cent. Atherosclerosis, however, can develop without increased blood pressure—to the extent of about 48 per cent in the series examined.

In essential hypertension and chronic glomerular nephritis, in which the blood pressure is high, the F.A.A. is far above the average (65 and 55.9 per cent, respectively). In acute infectious diseases the F.A.A., when it equaled the average F.A.A., was associated with a similar heart weight, and if the F.A.A. was lower, the heart weight was lower.

In carcinoma and tuberculosis, in which the heart weights were much lower than the average and were more nearly equal to the weights of the hearts with the smooth aortas, the F.A.A. was not lower than the average and in some instances was higher.

In diabetes mellitus the F.A.A. was much higher than the average, although the heart weights were lower than the average.

It follows that factors other than increased blood pressure must be present to incite the development of atherosclerosis.

Body weight and atherosclerosis showed no interconnection. In hypertension the body weight was somewhat greater than the average, but obesity was rarely present.

IV. PATHOGENESIS OF ATHEROSCLEROSIS OF AORTA AS BASED ON CHOLESTEROL METABOLISM, BLOOD PRESSURE, AND INFILTRATION AND EXPRESSION OF LIPOIDS

From chemical, experimental and pathologic studies, and from opinions gathered from the literature, it appears that the pathogenesis of atherosclerosis of the aorta is principally dependent on age, cholesterol metabolism and blood pressure. Other factors, such as heredity, nervous influences and glands of internal secretion, owe their importance to the manner in which they influence the aforementioned ones. As this paper is limited to the pathogenesis of atherosclerosis, the further remote factors are not discussed in great detail.

NORMAL CONSIDERATIONS

There is a great difference of opinion as to when the atherosclerotic process begins. According to Anitschkow and his school (Stuckey, Chalatow,[b] Wolkoff [b]), the hyperplasia and hypertrophy of the internal elastic membrane are dependent on the lipoid deposit in the aorta from infancy onward.

In a comparative study of the width of the aorta from the first year of life to 30 years (ascending stage of life) in both sexes of the white and colored races it was found that the average widths were similar until 11 years of age. After that time, the female aorta developed less rapidly. The progression of growth corresponded closely to the difference in physical activity of the two sexes that begins at about this age. It could only be inferred that the demands placed on the circulation determined the size and also the structure of the vessel (also Benninghoff).

The normal histologic structure of the aorta at the end of the ascending stage of life varies in different parts of the vessel. In the ascending portion the intima is narrow and the fibro-elastic layer is compact. Extending to the abdominal portion of the aorta the intima becomes thicker, mainly through the proliferation of the fibro-elastic layer, the elastic fibers of which are loosely arranged.

The amount of fat deposited in the intima of the aorta before 25 years of age is exceedingly small (Görög) and is out of proportion to the proliferation described.

Under normal conditions, in the ascending stage of life the serum of the blood stream infiltrating through the inner two thirds of the aorta may show a hindering of its lipoids at the elastic barriers. With contraction of the vessel in diastole there is an expression of this substance. The mechanism of expression is dependent on the nature of the elastic barriers, the width of the intima and the inequality of the contracting parts (part III). The lipoid deposit is dependent on the disproportion of the infiltration over expression under normal conditions. It is for this reason that muscular arteries, which have markedly developed internal elastic membranes that contract more vigorously than the other constituent parts of the vessel, express the lipoids more efficiently. For a similar reason, the arterioles, having lost their internal elastic membrane, are more susceptible to lipoid and hyaline infiltration as seen best in hypertension.

When there is a disturbance of the cholesterol metabolism, as in infancy, puberty and pregnancy or after some acute infections, a cholesterol deposit in the aorta occurs, owing to a disturbance of the infiltration-expression equilibrium in favor of the former. After a subsidence of the hypercholesteremia, the equilibrium is restored and the lipoid deposit disappears from the aorta (histiocytes also act as scavengers). Atherosclerosis of the aorta is thus rare in persons under 30 years of age.

AGE

After 30 years and more, particularly after 40 years, degenerative changes begin in the aorta as well as in other parts of the body. The

interstitial substance of the aorta ages as other colloids do with a decrease in hydration and a tendency to be transformed into a granular state (Wells). The elastic fibers, also being colloid masses, react in a similar way. These fibers decrease in number, and many are replaced by fibrous tissue, causing a dilatation of the vessel. Such changes having taken place, the serum cholesterol entering the aortic intima is deposited along the elastic barriers and remains there because the decreased elasticity prevents a thorough expression and favors stagnation, and because the dehydrated colloid favors a precipitation of the cholesterol esters as well as of calcium (Bürger and Schlomka, Wells).

The mechanism, however, requires other factors in addition to age, because without a disturbance of the cholesterol metabolism or an increased tension, an aorta may age without an appreciable lipoid deposit. This was clearly shown in a fair percentage of cases in which the dilatation of the aorta had taken place and yet the lipoid deposit was very small (part III). As the disturbances of the cholesterol metabolism as well as the increase in blood pressure are more prevalent with age, the incidence of atherosclerosis of the aorta also increases. It is significant that cases do exist in which physical colloidal changes have occurred and in which atherosclerosis is absent.

As one cannot measure the amount of aging of colloid in an aorta so is it impossible to determine the quality of the elastic tissue that one is endowed with. That heredity is an important factor is everywhere accepted (Jores, E. Kaufmann, Aschoff,[e, f] Janeway, T. DeWilliams). All other things being equal (environment, diet, etc.), the arteries of one person may age more rapidly than those of another. Similarly, in the same body, different vessels age at different rates (Wells, Wharton). For a large group of persons of the same race and sex living under like conditions the average aging of vessels was found to vary directly with age. That various diseases or malignant growths do not appreciably alter the degree of aging was shown in part III. One can then consider age as a variable constant in the development of atherosclerosis.

CHOLESTEROL METABOLISM

Whether disturbances of the cholesterol metabolism can be measured numerically only by the increase or the decrease of cholesterol in the blood, or whether there is an actual disturbance of the colloidal state of this substance, are questions yet to be answered. There is some evidence to show that variations in the colloidal properties of cholesterol esters can occur under similar temperatures (Chalatow[a]). Its determination in the body has not been definitely proved, so that at present the quantity of cholesterol in the blood is the only standard of measurement available. As the methods employed in the determination of the choles-

terol have been so numerous, the results are varied, and it cannot be definitely stated what the normal boundaries are.

Bürger found that normal persons show a marked hypercholesteremia (100 per cent increase) after ingestion of 5 Gm. of cholesterol dissolved in 100 cc. of oil. The peak is reached in four hours, and after twenty-four hours the cholesterol returns to normal (contested by Barreda). Because other authors, using questionable methods of examining the blood and preparing the patient, have obtained negative digestive lipemias in man, the evidence that exogenous cholesterol is concerned in the pathogenesis of atherosclerosis has been discredited. Further, it is definitely known that although the endogenous cholesterol is not directly dependent on the exogenous cholesterol, the former is related to the latter.

If a relatively short digestive hypercholesteremia occurs in persons who are accustomed to the ingestion of cholesterol-containing foods, most probably hypercholesteremia of longer duration follows in persons who are not accustomed to this type of food. The latter possibility was suggested in the young colored person who on changing his mode of living and diet acquired a hypercholesteremia, as was suggested by the early appearance of an arcus lipoides (part II). In such persons atherosclerosis sets in earlier than in the white people.

That the exogenous cholesterol may be of importance in atherosclerosis is also noted in comparative anatomy. The aves, particularly the parrot, are the only animals in which an atherosclerosis develops similar to that in man. The parrot is a meat and seed eater, substances containing cholesterol and neutral fats, respectively. It is admitted that age and the structure of the aorta of the parrot also play important rôles (Fox).

Endogenous cholesterol[4] may be influenced, as shown by hypercholesteremia, in pregnancy, in retention of the cholesterol through blocking of the excretion of bile, in the transportation of cholesterol, as in inanition and the diseases leading to it (diabetes mellitus, tuberculosis, nephritis, carcinoma), in the liberation of cholesterol through cytolysis (acute infections, nephrosis, tuberculosis, carcinoma), by narcosis, and by glands of internal secretion.

How these factors act has been discussed elsewhere (parts II and V[5]). When a hypercholesteremia does occur, the inclination to atherosclerosis, as determined by the fat angle of the aorta (F.A.A.), increases (part I). In cases in which only the cholesterol metabolism is affected, as in diabetes mellitus, the hyperlipocholesteremia augments the inclination to

4. By endogenous cholesterol is meant that cholesterol that is not derived directly from the food.

5. Part V will be published in the December issue of the ARCHIVES.

atherosclerosis (F.A.A., 59.7°, as compared with the average, 45.5°). In the one case of lipoid nephrosis (a colored man aged 55) the F.A.A. was 62° (average, 48.2°). Although the incidence of atherosclerosis in diabetes is known to be high, in lipoid nephrosis the condition is not common. This is probably because nephrosis occurs as a rule in young persons and is not protracted over a long period.

What change occurs in the cholesterol metabolism with age is not known. Whether with age there is an actual increase in the blood cholesterol, or whether the digestive lipemia is accentuated, or whether a disturbance of the cholesterol metabolism occurs without an increase in the blood cholesterol is yet to be determined. Some authors have even reported a decrease in blood cholesterol in older persons. It must be remembered, however, that other conditions influencing the cholesterol metabolism also increase with age, such as diabetes mellitus, carcinoma and diseases in general. A slight disturbance of the cholesterol metabolism with age is more serious than a similar disturbance in youth in the development of atherosclerosis, as the "binding" of cholesterol is more effective with age.

How does cholesterol, especially its esters, affect the development of atherosclerosis? Aschoff,[a, b, c] Kawamura, Windaus and Schönheimer [a, c, d] have definitely proved that the cholesterol esters constitute the greatest part of the lipoid deposit in the aorta (57 per cent). This substance appears in the intima of the aorta long before degenerative changes can be seen with the microscope (Aschoff,[a, b] Zinzerling,[a, b] Görög). In histologic studies in human beings and cholesterol-fed rabbits it was found that the cholesterol esters stimulated histiocytic proliferation in the aorta as well as in the liver and kidney (Rosenthal; also McMeans, Stuckey, Wolkoff, Klotz and Manning). Anitschkow and his school described fibrous and elastic tissue proliferation as well as scar formation in the aortic intima after years of cholesterol feeding. Chalatow explained the cirrhosis of the liver that occurred in some cholesterol-fed rabbits on the basis of a change in the type of cholesterol, which then became more irritative (also Bailey [c]). What action the various cholesterol esters (palmitic, stearic and oleic) found in the blood and the aorta have is not known.

When one considers that the amount of fat in the aorta is almost directly proportional to the severity of the atherosclerosis (part I), it seems that the amount of fat determines the severity of the lesions and not vice versa. If one takes, e. g., fibrosis and scar formations in other parts of the body, the amounts of fat present in these lesions are usually small and depend as a rule on the necrosis of the constituents. In the aorta, although necrosis is also found and may accentuate the lipoid deposit, cholesterol esters are found long before the occurrence

of necrosis. It is true that a precipitation of the lipoids may occur as the result of aging of the colloid there (a submicroscopic phenomenon), but once the lipoid is deposited, it sets up an irritative action and probably accounts for the lesions that are known as atherosclerosis. When one considers that as much as 3 Gm. of fat may be deposited in the aortic intima, an irritation by the same is not difficult to conceive. Lipoids are found deposited to a slight degree in old dilated aortas, but here the senile sclerotic changes predominate. The latter condition is not atherosclerosis but senile sclerosis.

When cholesterol is deposited in an adult aorta at a rapid pace it effects the blocking of the blood supply to that part, and necrosis may follow. The latter in turn favors more deposit of lipoid as well as of hyalin and calcium (Wells, Barr). The intima covering a lipoid node undergoes pressure atrophy or necrosis. If the process is not rapid, the incrustation of calcium or hyalin in this atrophic intima follows and a calcific or hyaline plaque results. If the process of lipoid deposit is rapid, the overlying intima becomes necrotic and is swept away by the current of the blood stream, forming an atheromatous ulceration. As calcification is considered a secondary process, the mechanism of its deposition is not discussed at full length (for detailed studies, Barr, Wells and Schönheimer [e] may be referred to).

The older the subject the greater is the susceptibility to ulceration, while the younger the subject the greater is the inclination to fibrosis and hyalinization. In the latter, the expression mechanism is more efficient and the precipitation of the lipoid is less marked.

The sites of deposition of the cholesterol esters are to a great extent dependent on the structure of the intima and especially the elastic membranes. In the abdominal portion of the aorta the atherosclerotic process is more common, and this is accounted for by the loosely arranged elastic fibers of the fibro-elastic layer, which forms a barrier for the infiltration as well as for the expression of lipoids. Similarly, node and plaque formation is usually found about points where branches issue, because of a thickened intima there and a loose arrangement of the elastic fibers (Benninghoff). As in human beings, so in experimental animals, this has been found not only in the aorta but also where blood vessels divide, as at the division of the carotid artery.

The deposition of cholesterol is found in the same locations in youth as in age because of the peculiar structure of the aorta. Because in youth the infiltration and expression of lipoids is held in an equilibrium, and because the cholesterol is not "bound," atherosclerosis does not develop, while with age the "binding" of the cholesterol as well as the inefficient expression of the same accounts for the high incidence of atherosclerosis.

BLOOD PRESSURE

The action of the blood pressure may be that of forcing the lipoids into the aorta at a greater pace (Aschoff,[e] Ribbert, Hueck, Stumpf) or that of hastening the aging process.

That increased pressure favors lipoid deposition is best seen from the infrequency of lipoid deposits in veins or in the pulmonary artery. With increase of the interpulmonary pressure, lipoid deposit in the pulmonary artery occurs readily (Sternberg, Moschcowitz,[a, b] Rosenthal) and similarly with increased pressure in the veins (Moschcowitz [a]).

In the greater circulation, increased blood pressure favors the development of atherosclerosis to a marked degree. The F.A.A. in essential hypertension was found to be 63° as compared with the average of 48°. There were some cases in which increased blood pressure did not lead to atherosclerosis. In a white man 30 years of age with an essential hypertension and a heart weight of 760 Gm., the amount of fat in the aorta was minimal (0.133 Gm.). However, the percentage of such cases was small (7 per cent). When an increase of the blood pressure had been prolonged, atherosclerotic changes of the aorta followed (Lange,[b] Moschcowitz [a]).

The question of determining the "normal" blood pressure is difficult. Thus, for persons of the white civilized race living under similar conditions, the blood pressure is much higher than for primitive races. Among the white civilized people, a change of environment and diet seems to be accompanied by a lowered blood pressure. Saile found that monks who are strictly vegetarian (excluding also eggs and butter) and who live entirely secluded (rarely talking) have a much lower blood pressure than monks who live on the average diet and go among their people. Similarly, Donnison found that the average blood pressure for the East African Negro (105 systolic and 67 diastolic at 60 years) was lower than that for the white race (140 systolic and 90 diastolic at 60 years). The colored race living in Chicago have a higher incidence of hypertension than the white race (Jaffé [c]).

Romberg [b] considers 160 systolic and 100 diastolic as the boundary of hypertension for the white race. This high "normal" value, in truth, should be considered as representing hypertension and may partially account for the high frequency of atherosclerosis in the white race.

The increased inclination to hypertension, especially of the malignant type, in the young colored persons dying at the Cook County Hospital may explain in part the increased inclination to atherosclerosis.

Local increases in blood pressure may also favor increased lipoid deposit. Thus, where vessels come in contact with bony parts, the resistance is greater and the deposit of lipoids is augmented. The

posterior wall of the aorta (Ophüls, Westenhöffer), the dural vessels (Lauda, Erdheim) and the internal carotid artery in the canal of the temporal bone are examples.

COMBINATION FORMS (BLOOD PRESSURE AND CHOLESTEROL METABOLISM DISTURBANCES)

It has been shown that marked disturbances of the cholesterol metabolism (diabetes mellitus and lipoid nephrosis) or marked increases of the blood pressure (essential hypertension) greatly increase the inclination to atherosclerosis. Combinations of these disturbances correspondingly alter this tendency.

In tuberculosis and carcinoma, in which there is a slight disturbance of the cholesterol metabolism but in which the blood pressure is lower than the average, the fat angle of the aorta (F.A.A.) is either lower than, or equal to, the average (part II). In acute infectious diseases, in which the cholesterol metabolism is only slightly disturbed for a short period of time, the F.A.A. is higher or lower, depending on the blood pressure. In chronic glomerular nephritis in which the cholesterol of the blood reaches a high "normal" or may be definitely increased, and in which the blood pressure is increased, the F.A.A. is increased. When both hypertension and marked cholesterol disturbances occur (diabetes mellitus with hypertension), the inclination to atherosclerosis is the highest (F.A.A., 76.8°; average, 48.5°).

The inclination to atherosclerosis is equally dependent on the cholesterol metabolism and hypertension, age being the variable constant. One cannot say that one or the other factor is capable of producing atherosclerosis alone, as the maintenance of blood pressure and cholesterol in the blood must always be contended with.

SUMMARY

The factors of age, cholesterol metabolism and blood pressure have been separately discussed in their relationship to atherosclerosis.

Although not all people age at a like rate, for a large homogeneous group living under similar conditions, the factor of age has been considered as a variable constant. Blood cholesterol and arterial tension also show a tendency to be augmented with senescence, but not necessarily. If it were possible to conceive that the aforementioned factors could exist alone, i.e., age, disturbance in the cholesterol metabolism and arterial tension, none could produce atherosclerosis alone.

Cholesterol, especially its esters, is of primary importance in atherosclerosis. Age and arterial tension check or augment the development of atherosclerosis. As it happens, age is inevitable and thus plays an exceedingly important rôle in the development of atherosclerosis, perhaps

as important as that of disturbances of the cholesterol metabolism and arterial tension combined. But atherosclerosis can occur in very young persons in whom a disturbance of the cholesterol metabolism exists without hypertension (as early as 10 years of age in persons with diabetes or lipoid nephrosis—Joslin). Hypertension alone will not lead to atherosclerosis, as has been shown experimentally and in the text. But as it is more prevalent in the descending stage of life it, too, plays a deciding rôle.

GENERAL SUMMARY

In a chemical analysis of 500 aortas of the white and colored races it was found that the fat content was not only directly proportional to age but also to the severity of atherosclerosis.

Because in a large group of cases the amount of fat in the aorta followed a regular ascent with age, the angle of inclination was designated as the fat angle of the aorta (F.A.A.), or the inclination to atherosclerosis. The deducted formula is:

$$\text{tangent F.A.A.} = \frac{(\text{fat in grams} \times 100)}{15} - 2.$$

The F.A.A. of all the cases studied was 49.1°, which was interpreted as a slight to moderate atherosclerosis.

Differences in the F.A.A. for the white and colored races and for the sexes suggested that the factor of age alone was not paramount in the production of atherosclerosis.

Because atherosclerosis occurred earlier in the colored race than in the white race, and because arcus lipoides was also prevalent in the former and not in the latter, it was deducted that the cholesterol metabolism may have played a rôle in the production of atherosclerosis. On the basis of the work of Joël, arcus lipoides occurring in young persons is associated with a hypercholesteremia. To substantiate this point further it was found that atherosclerosis occurred more frequently in diseases in which a hypercholesteremia was present (diabetes mellitus and lipoid nephrosis when long protracted). In carcinoma and tuberculosis, in which the cholesterol metabolism is less affected, the incidence of atherosclerosis was less. Furthermore, in compiling the literature relative to atherosclerosis among primitive races and in animals it was found that when atherosclerosis occurred, cholesterol and fats were present in the diet.

Measuring the aging of the aorta by its width showed that age played an important rôle in the development of atherosclerosis, but cases occurred in which aortic dilatation was not associated with atherosclerosis (up to 27 per cent).

It was inferred that age alone may lead to a senile sclerosis of the aorta but not to an atherosclerosis.

Arterial tension as determined by the weight of the heart was an important factor in the production of atherosclerosis, but atherosclerosis and hypertension are not synonymous. Indeed in 48 per cent of the cases, atherosclerosis occurred without hypertension.

In essential hypertension and in glomerular nephritis the F.A.A. was high, while in carcinoma and tuberculosis, in which the arterial tension was lower, the F.A.A. was lower but not correspondingly so. In acute infectious diseases the F.A.A. was proportional to the heart weights.

The development of the aorta from birth to 30 years was given, and it was inferred that the hyperplasia and hypertrophy of the intima were a functional response and not related to the fat deposit.

From morphologic and experimental evidence the deposit of lipoids was found to be closely related to the structure of the vessel and to the infiltration and expression of fats; the infiltration is dependent on the cholesterol in the serum, the blood pressure and the nature of the limiting membranes, while the expression of lipoids is dependent on the nature of the elastic barriers, the width of the intima and the inequality of the contracting parts.

The thickness of the intima of the abdominal portion of the aorta and the loose arrangement of the fibro-elastic layer were given as a partial cause for the higher incidence of atherosclerosis there.

The relatively thin intima and the well developed internal elastic membranes of muscular arteries were suggested as favoring expression of lipoids and therefore the rarity of lipoid deposit in these vessels.

The reaction of the aortic intima to cholesterol esters in young adults is that of fibrous tissue proliferation and hyalinization, while in older persons ulceration is more prevalent.

LITERATURE

Adler, I.: J. Exper. Med. **20**:93, 1914.

Albutt, Clifford: Diseases of the Arteries, New York, The Macmillan Company, 1915.

Alvarez, W. C.; Wiezen, R., and Mahoney, L. J.: Arch. Int. Med. **26**:381, 1923.

Anitschkow, N.: (*a*) Beitr. z. path. Anat. u. z. allg. Path. **51**:379, 1913; (*b*) Virchows Arch. f. path. Anat. **249**:73, 1924; (*c*) Experimental Arteriosclerosis in Animals, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 271.

——and Chalatow, S.: Centralbl. f. allg. Path. u. path. Anat. **24**:1, 1913.

Arndt, H. J.: Ztschr. f. d. ges. exper. Med. **54**:391, 1927.

Aschoff, A.: Ueber Entwicklungs-, Wachstums- und Altersvorgänge in den Gefässen, Jena, Gustav Fischer, 1909.

Aschoff, L.: (*a*) Verhandl. d. deutsch. path. Gesellsch. **10**:166, 1906; (*b*) Beitr. z. path. Anat. u. z. allg. Path. **47**:1, 1910; (*c*) Lectures in Pathology, New York, Paul B. Hoeber, Inc., 1924; (*d*) Arch. ital. di sc. med. **50**:1, 1927; (*e*) Beihft. z. med. Klin. **1**:1, 1930; (*f*) in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.

Bailey, C. H.: (*a*) Proc. Soc. Exper. Biol. & Med. **12**:68, 1914; (*b*) **13**:60, 1915; (*c*) J. Exper. Med. **23**:69, 1916.
Barr, D. P.: Physiol. Rev. **12**:593, 1932.
Barreda, P.: Klin. Wchnschr. **13**:290, 1934.
Beitzke, H.: Virchows Arch. f. path. Anat. **267**:625, 1928.
Beneke, R.: Beitr. z. path. Anat. u. z. allg. Path. **87**:285, 1931.
Benninghoff, A.: Blutgefässe und Herz, Handbuch der mikroskopischen Anatomie, Berlin, Julius Springer, 1930, vol. 6, pt. I.
Benson, R. D.; Smith, K. S., and Semenov, H.: Arch. Path. **12**:925, 1931.
Beumer, H.: Ztschr. f. d. ges. exper. Med. **35**:328, 1925.
Björling, E.: Virchows Arch. f. path. Anat. **205**:71, 1911.
Blackford, J. M.; Bowers, J. M., and Baker, J. W.: J. A. M. A. **94**:328, 1930.
Boinet, E., and Romary: Arch. de méd. expér. et d'anat. path. **9**:902, 1897.
Bramwell, C.: Physical Properties of Arteries in Health and Diseases, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.
Bürger, M.: Ergebn. d. inn. Med. u. Kinderh. **34**:583, 1928.
——and Habs, H.: Klin. Wchnschr. **6**:2221, 1927.
——and Schlomka, G.: Ztschr. f. d. ges. exper. Med. **55**:287, 1927.

Camac, C. N. B.: Am. J. M. Sc. **129**:845, 1905.
Cellina, M.: Cuore e circolaz **15**:506, 1931.
Chalatow, S. S.: (*a*) Virchows Arch. f. path. Anat. **207**:452, 1912; (*b*) **272**:691, 1929.
Chauffard, A.; Laroche, G., and Grigart, A.: Obstretique **4**:481, 1911.
——Richet, C., and Grigaut, A.: Compt. rend. Soc. de biol. **70**:317, 1911.
Chuma, M.: Virchows Arch. f. path. Anat. **272**:691, 1929.
Cirio, L.: Virchows Arch. f. path. Anat. **269**:739, 1928.
Cramer, H.: Virchows Arch. f. path. Anat. **230**:46, 1921.

Dewey, K.: Arch. Int. Med. **17**:575, 1916.
DeWilliams, S.: Heredity Aspects of Arterial Hypertension in Relation to Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 537.
Diehl, H. S., and Sutherland, K. H.: Arch. Int. Med. **36**:151, 1925.
Donnison, C. P.: Lancet **1**:6, 1929.
Duguid, J. B.: J. Path. & Bact. **29**:371, 1926.

Erdheim, J.: Jahrb. f. Psychiat. u. Neurol. **39**:322, 1919.

Fahr, T.: (*a*) Frankfurt. Ztschr. f. Path. **9**:15, 1911; (*b*) Virchows Arch. f. path. Anat. **239**:41, 1922.
Foster, J. H.: Arch. Int. Med. **40**:38, 1927.
Fox, W.: Arteriosclerosis in Mammals and Birds, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 153.
Freund, H., and König, W.: Arch. f. exper. Path. u. Pharmakol. **33**:317, 1928.

Gager, L. T.: J. A. M. A. **99**:82, 1928.
Gewert, M.: Veröffentl. a. d. Kriegs u. Konstitutionspath. **23**:1, 1929.
Glasunow, M.: Virchows Arch. f. path. Anat. **261**:837, 1926.
Görög, D.: Virchows Arch. f. path. Anat. **287**:603, 1933.
Grigaut, M.: Le cycle de la cholesterinémie, Paris, Steinheil, 1913.
Grundstein, N.: Arch. f. mikr. Anat. **47**:583, 1896.
Gull, W., and Sutton, H.: Med.-Chir. Tr., London **55**:273, 1972.
György, P.: Klin. Wchnschr. **3**:483, 1924.

Hackel, W. M.: Ztschr. f. d. ges. exper. Med. **72**:762, 1930.
Hesse, M.: Virchows Arch. f. path. Anat. **261**:225, 1926.
Hirsch, C.: Deutsche med. Wchnschr. **38**:1817, 1913.
Hoppe-Seyler, F.: Medizinisch-klinische Untersuchungen aus dem Laboratorium für angewandte Chemie zu Tübingen, Berlin, A. Hirschwald, 1866-1871, vol. 6, p. 593.
Hueck, W.: Beitr. z. path. Anat. u. z. allg. Path. **66**:330, 1920.
Hunt, H. M.: New England J. Med. **201**:659, 1929.
Hurxthal, L. M.: Arch. Int. Med. **52**:86, 1933.
Ignatowski, A.: Virchows Arch. f. path. Anat. **198**:248, 1909.
Irsigler, F. H.: Beitr. z. path. Anat. u. z. allg. Path. **85**:221, 1930.
Ismail, Abd-el. Aziz: Lancet **2**:275, 1928.
Jaffé, R. H.: (*a*) Klin. Wchnschr. **10**:2081, 1931; (*b*) Centralbl. f. allg. Path. u. path. Anat. **55**:209, 1932.
——and Sternberg, H.: Med. Klin. **51**:1311, 1919.
Janeway, T.: Clinical Study of Blood-Pressure, New York, D. Appleton and Company, 1904.
Joël, E.: Klin. Wchnschr. **3**:269, 1924.
Jores, L.: Arteriosklerose, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, p. 703.
Joslin, E. P.: Ann. Clin. Med. **5**:1061, 1927; Ann. Int. Med. **4**:54, 1930.
Kani, I.: Virchows Arch. f. path. Anat. **201**:45, 1910.
Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. de Gruyter & Co., 1931, vol. 1.
Kaufmann, L.: Zur Frage der Aorta Angusta, Inaug. Diss., Freiburg, 1919.
Kawamura, R.: Neue Beiträge zur Morphologie und Physiologie des Cholesterinstoffwechsels, Jena, Gustav Fischer, 1927.
Key-Aberg, A.: Ueber den Bau der Tunica intima der Aortenwand bei dem erwachsenen Menschen, Biol. Intersuch. **1**:27, 1881.
Klotz, O.: (*a*) J. Exper. Med. **8**:504, 1904; (*b*) J. A. M. A. **58**:1971, 1912; (*c*) J. M. Research **28**:157, 1916.
——and Manning, M. F.: J. Path. & Bact. **16**:211, 1911.
Knack, A., and Neumann, J.: Deutsche med. Wchnschr. **43**:901, 1917.
Knauer, H.: Klin. Wchnschr. **8**:1745, 1929.
Kolen, A. A.: Virchows Arch. f. path. Anat. **272**:679, 1929.
Krause, K.: Beitr. z. path. Anat. u. z. allg. Path. **70**:121, 1922.
Kuczynski, B.: Klin. Wchnschr. **4**:39, 1925.
Labbé, M., and Heitz, J.: Ann. de méd. **18**:108, 1925.
Lange, F.: (*a*) Virchows Arch. f. path. Anat. **248**:465, 1924; (*b*) Hypertension in Relation to Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 503.
——and Webner, E.: Deutsches Arch. f. klin. Med. **160**:45, 1928.
de Langen, G. D.: Nederl. tijdschr. v. geneesk. **65**:3056, 1921.
Lauda, E.: Beitr. z. path. Anat. u. z. allg. Path. **68**:180, 1921.
Lefkowitz, M., and Rosenberg, D.: Frankfurt. Ztschr. f. Path. **34**:174, 1926.
Levine, V., and Carr, J.: Arch. Int. Med. **52**:429, 1933.
Lotzmann, L. A.: Virchows Arch. f. path. Anat. **256**:117, 1925.
Löwenthal, K.: Verhandl. d. deutsch. path. Gesellsch. **20**:137, 1925.
Lubarsch, O.: Ueber Arteriosklerose, Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte, Münster, 1912, vol. 84, p. 2.

MacCallum, W. G.: Acute and Chronic Infections as Etiological Factors in Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 355.
McCollum, E. V., and Simmonds, N.: The Newer Knowledge of Nutrition, New York, The Macmillan Company, 1929.
McMeans, J. N.: J. M. Research **33**:475 and 481, 1916.
——and Klotz, O.: J. M. Research **34**:41, 1916.
Marchand, F.: Verhandl. d. Kong. f. inn. Med. **21**:23, 1904.
Mjassnikow, A. L.: Ztschr. f. klin. Med. **103**:267, 1926.
Moissejeff, E.: Ztschr. f. d. ges. exper. Med. **60**:611, 1928.
Moschcowitz, E.: (*a*) Am. J. M. Sc. **178**:244, 1929; (*b*) Virchows Arch. f. path. Anat. **283**:282, 1932.
Müller, W.: Massenverhältnisse des menschlichen Herzens, Leipzig, Leopold Voss, 1883.
Murata, M., and Kataoka, S.: Tr. Jap. Path. Soc. **7**:27, 1917.

Neumann, R.: Frankfurt. Ztschr. f. Path. **42**:319, 1931.
Newburgh, L. H., and Clarkson, S.: Arch. Int. Med. **31**:653, 1923.
Newmann, E. T.: Arch. f. Schiffs- u. Tropen-Hyg. **34**:183, 1930.
Nieberle, K.: Verhandl. d. deutsch. path. Gesellsch. **25**:291, 1930.
Nordmeyer, N.: Beitr. z. path. Anat. u. z. allg. Path. **86**:149, 1931.
Nuzum, F. R.; Seegal, B.; Garland, R., and Osborne, M.: Arch. Int. Med. **37**: 733, 1926.

Okunoff, N.: Virchows Arch. f. path. Anat. **259**:685, 1926.
Ophüls, W.: The Pathogenesis of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 249.

Pallaske, G.: Frankfurt Ztschr. f. Path. **40**:64, 1930.
Palmer, R. S.: J. A. M. A. **94**:694, 1930.
Petroff, J. R.: Beitr. z. path. Anat. u. z. allg. Path. **71**:115, 1923
Pfleidner, E.: Virchows Arch. f. path. Anat. **284**:154, 1932.
Pribram, H.: Prag. med. Wchnschr. **37**:205, 1912.

Raab, W.: (*a*) Hormone und Stoffwechsel, Munich, Dr. F. P. Datterer & Cie, 1926. (*b*) Med. Klin. **14-15**:1, 1932.
Ranke, O.: Beitr. z. path. Anat. u. z. allg. Path. **75**:269, 1926.
Reuterwall, O. P.: Acta med. Scandinav. **55**:1, 1921.
Ribbert, H.: Verhandl. d. deutsch. path. Gesellsch. **8**:168, 1904; Deutsche med. Wchnschr. **44**:953, 1918.
Richter-Quittner, M.: Wien. Arch. f. inn. Med. **1**:425, 1920.
Rössle, R., and Roulet, F.: Mass und Zahl in der Pathologie (Pathologie und Klinik), Berlin, Julius Springer, 1932, vol. 5.
Roger, L.: Glasgow M. J. **103**:1, 1925.
Rohrschneider, W.: Virchows Arch. f. path. Anat. **256**:139, 1925.
Romberg, E.: (*a*) Deutsche med. Wchnschr. **31**:1377, 1905; (*b*) Lehrbuch der Krankheiten des Herzens, Stuttgart, Ferdinand Enke, 1921.
Rosenthal, F., and Holzer, P.: Arch. f. klin. Med. **135**:257, 1921.
——and Patrzek, F.: Deutsche med. Wchnschr. **45**:1037, 1919.
Rosenthal, S. R.: Arch. Path. **10**:717, 1930.
Rothschild, M. A.: Beitr. z. path. Anat. u. z. allg. Path. **60**:39, 1915.
Rouzaud and Cabanis: Compt. rend. Soc. de biol. **74**:469, 1919.
Rühl, A.: (*a*) Deutsches Arch. f. klin. Med. **156**:13, 1927; (*b*) Pharmakol. u. therap. Rundschau **140**:257, 1929.

Ruffer, M. A.: Studies in Paleopathology of Egypt, Chicago, University of Chicago Press, 1921.

Saile, F.: Med. Klin. **26**:929, 1930.
Saltykow, S.: Beitr. z. path. Anat. u. z. allg. Path. **43**:147, 1908.
Scheel, O.: Virchows Arch. f. path. Anat. **191**:135, 1908.
Schmidtmann, M., and Huttich, M.: Virchows Arch. f. path. Anat. **267**:601, 1928.
Schönheimer, R.: (*a*) Virchows Arch. f. path. Anat. **249**:1, 1924; (*b*) **251**:732, 1924; (*c*) Ztschr. f. physiol. Chem. **160**:61, 1926; (*d*) **177**:143, 1928; (*e*) Klin. Wchnschr. **43**:1793, 1932.
Schultz, A.: Virchows Arch. f. path. Anat. **239**:415, 1922.
Schultze, W. H.: Ergebn. d. allg. Path. u. path. Anat. **13**:253, 1909.
Shapiro, P. F.: Arch. Int. Med. **48**:199, 1931.
Shapiro, S.: J. Exper. Med. **45**:595, 1927.
Soli, V.: Ann. di clin. med. **14**:251, 1924.
Ssokoloff, N. A.: Virchows Arch. f. path. Anat. **245**:203, 1923.
Ssolowjew, A.: (*a*) Virchows Arch. f. path. Anat. **241**:1, 1923; (*b*) **250**:359, 1924; (*c*) Ztschr. f. d. ges. exper. Med. **69**:94, 1930.
Starkodamski, L. M.: Zur Frage ueber die experimentelle Arteriosklerose, Inaug. Dissert. St. Petersburg, 1909.
Steinbiss, W.: Virchows Arch. f. path. Anat. **212**:151, 1913.
Stepp, W.: Beitr. z. path. Anat. u. z. allg. Path. **69**:233, 1921.
Sternberg, V.: Beitr. z. path. Anat. u. z. allg. Path. **82**:307, 1929.
Stocks, Percy: Race and Climate as Possible Factors in Arteriosclosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 195.
Strauch, C.: Beitr. z. path. Anat. u. z. allg. Path. **61**:536, 1916.
Stucky, N. W.: Veränderungen der Kaninchenaorta unter dem Einfluss der Fütterung mit animalischer Nahrung, Inaug. Dissert., St. Petersburg, 1910; Centralbl. f. allg. Path. u. path. Anat. **21**:668, 1910.
Stumpf, A.: Beitr. z. path. Anat. u. z. allg. Path. **59**:390, 1914.
Suter, F.: Arch. f. exper. Path. u. Pharmakol. **39**:289, 1897.
Sydenstricker, E.: Statistical Study of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 131.

Thannhauser, S. J.: (*a*) Deutsches Arch. f. klin. Med. **141**:290, 1922-1923; (*b*) Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, Munich, J. F. Bergmann, 1929.
Thérèse, L.: Rev. de méd. Paris **13**:123, 1893.
Thölldte, M.: Beitr. z. path. Anat. u. z. allg. Path. **77**:61, 1927.
Thoma, A.: Virchows Arch. f. path. Anat. **204**:1, 1911.
Thomas, W. A.: J. A. M. A. **88**:1559, 1927
Torhorst, H.: Beitr. z. path. Anat. u. z. allg. Path. **36**:210, 1904.
Tsunoda, T., and Umehara, N.: Tr. Jap. Path. Soc. **6**:90, 1916.
Tung, Chen-Lang: (*a*) Chinese J. Physiol. **1**:93, 1928; (*b*) **4**:117, 1930.

Versé, M.: (*a*) Beitr. z. path. Anat. u. z. allg. Path. **63**:789, 1916; (*b*) Deutsche med. Wchnschr. **51**:49, 1925.
Virchows, R.: Wien. med. Wchnschr. **6**:809, 1856.
Voigt, H.: Der Aufbau der normalen Aorta, Inaug. Dissert., Marburg, 1904.
Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, in von Bergmann, G., and Staehelin, R.: Handbuch der innerer Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 1.

Wacker, L.: Ztschr. f. physiol. Chem. **80**:383, 1912.
——and Hueck, W.: Arch. f. exper. Path. u. Pharmakol. **71**:373, 1912-1913.
Weiss, S., and Minot, G. R.: Nutrition in Relation to Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, p. 233.
Wells, H. G.: The Chemistry of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.
Westenhöfer, P.: Deutsche med. Wchnschr. **48**:518, 1922.
Wharton, A. S.: Old Age, the Major Involution, New York, Paul B. Hoeber, Inc., 1929.
Widal, F.; Weil, A., and Laudat, M.: Semaine méd. **32**:529, 1912.
Wilheim, R., and Fuchs, G.: Biochem. Ztschr. **247**:297, 1932.
Windaus, A.: Ztschr. f. physiol. Chem. **67**:174, 1910.
Wolkoff, K.: (*a*) Virchows Arch. f. path. Anat. **256**:751, 1925; (*b*) Beitr. z. path. Anat. u. z. allg. Path. **85**:386, 1930.
Wyckoff, J.: The Treatment of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.

Yuasa, D.: Beitr. z. path. Anat. u. z. allg. Path. **80**:570, 1928.

Zeek, P.: Am. J. M. Sc. **184**:350, 1932.
Zinzerling, W. D.: (*a*) Virchows Arch. f. path. Anat. **255**:676, 1925; (*b*) Beitr. z. path. Anat. u. z. allg. Path. **88**:241, 1932.

Case Reports, Laboratory Methods and Technical Notes

HAND-SCHÜLLER-CHRISTIAN'S DISEASE AND TUBERCULOSIS

HUGH G. GRADY, M.D., AND HAROLD L. STEWART, M.D., PHILADELPHIA

Excellent reviews of the clinical, biochemical and morphological manifestations of Hand-Schüller-Christian's disease or, as Chester [1] designates the condition, lipoid-granulomatosis, have recently been published by Lichty,[2] Merritt and Paige,[3] Davison,[4] Pick,[5] Chiari,[6] Sosman,[7] Henschen,[8] Kleinmann [9] and Ighenti.[10] No attempt will be made to review the literature except as it pertains to the case under consideration. The features of particular interest in this case include changes in the lymph nodes, spleen and certain areas of the bone marrow resembling those in the group of nonlipoid histiocytosis described by Foot and Olcott.[11] In addition the lungs and mediastinal lymph nodes contained tuberculous foci which were frequently cleancut and separate but which at other times exhibited some overlapping with the granulomatous lesions of xanthomatosis. The latter lesions were widespread, often incipient, just as specific as the tuberculous changes, and occurred in such unusual situations as the hypophysis, liver, spleen and lymph nodes. Death occurred under ether anesthesia, which fact, coupled

From the Pathological Laboratories of the Jefferson Medical College and Hospital, the Jefferson Hospital Tumor Clinic and the Philadelphia General Hospital.

1. Chester, W.: Virchows Arch. f. path. Anat. **279**:561, 1930. Chester, W., and Kugel, V. H.: Arch. Path. **14**:595, 1932.
2. Lichty, D. E.: Arch. Int. Med. **53**:379, 1934.
3. Merritt, K. K., and Paige, B. H.: Am. J. Dis. Child. **46**:1368, 1933.
4. Davison, C.: Arch. Neurol. & Psychiat. **30**:75, 1933.
5. Pick, L.: Am. J. M. Sc. **185**:601, 1933.
6. Chiari, H.: Verhandl. d. deutsch. path. Gesellsch. **25**:347, 1930; Ergebn. d. allg. Path. u. path. Anat. **24**:396, 1931; Virchows Arch. f. path. Anat. **288**:527, 1933.
7. Sosman, M. C.: Am. J. Roentgenol. **23**:581, 1930; J. A. M. A. **98**:110, 1932.
8. Henschen, F.: Acta pædiat. (supp. 6) **12**:1, 1931.
9. Kleinmann, H.: Virchows Arch. f. path. Anat. **282**:613, 1931.
10. Ighenti, W. K.: Virchows Arch. f. path. Anat. **282**:585, 1931.
11. Foot, N. C., and Olcott, C. T.: Am. J. Path. **10**:81, 1934.

with the changes in the suprarenal and thymus glands, emphasizes one of the risks involved when operative procedures are contemplated in persons with Hand-Schüller-Christian's disease.

REPORT OF A CASE

In a white girl aged 3 years, pain, tenderness and discharge from both ears developed in May 1931. A partial facial paralysis appeared on the left side and subsequently cleared up; later a complete and permanent paralysis developed on the right side of the face. She was treated with roentgen therapy, and a right-sided simple mastoidectomy was done. On microscopic examination of tissue removed from the mastoid process a diagnosis of sarcoma was made. A second biopsy specimen was examined by Dr. Arnold Rich of Baltimore who favored the diagnosis of Hand-Schüller-Christian's disease. A large nodule which appeared below the right ear in March 1932 and similar lesions developing in the left ear in June of the same year responded well to radium therapy. A left-sided simple mastoidectomy was done subsequently and revealed a condition similar to that encountered on the right side.

She was admitted to Jefferson Medical College Hospital on Oct. 18, 1932, with a mass of granulation tissue in the right posterior auricular region, bilateral open sinuses in the mastoid areas, a discharge from both ears and a right-sided facial paralysis. On exploring the left mastoid area, all landmarks, including the posterior osseous wall of the bony canal, were found to be destroyed, and the dura was covered with fibrous granulation tissue. A radical operation was done, and the tissue removed consisted of vascular cellular granulation tissue with many inflammatory cells, chiefly polymorphonuclear leukocytes and large mononuclear cells. No exophthalmos or other abnormality was noted on ophthalmologic examination on Jan. 17, 1933. On roentgenographic examination (Jan. 24, 1933) the middle fossa of the skull appeared depressed, and a sharply defined area of osseous destruction, about the size of a silver dollar, was demonstrated in the lower posterior portion of the right parietal bone. This bony defect, which had not increased in size by April 9, 1933, was incised and drained, and smears of the material obtained showed many pus cells, gram-positive cocci and gram-negative rods. Staphylococcus albus and Streptococcus nonhaemolyticus grew in cultures planted with this material. There was a slight degree of secondary anemia. The urine contained a faint trace of albumin on several occasions, but no records of the urinary output were kept. The blood contained 59 Mg. of sugar per hundred cubic centimeters (Benedict method; normal, from 60 to 100 mg. per hundred cubic centimeters); the blood cholesterol was not studied.

The enlarged cervical nodes regressed somewhat under roentgen therapy, but the other lesions and the patient's general condition remained about the same. Death occurred suddenly under ether anesthesia during an attempted tonsillectomy on June 8, 1933.

Postmortem Examination (Six Hours After Death).—The head was enlarged, and the face presented a square appearance. There were numerous superficial petechial hemorrhages in the skin of the abdomen and recent incisions lined by dark necrotic material along the angle of each jaw and above and behind the right ear. Purulent fluid was observed exuding from each external auditory meatus.

No gross lesions were observed in the brain. The dura in the immediate vicinity of the sella turcica contained several small yellowish nodules, and its inner surface was covered by a yellowish-brown, granular deposit which could be scraped away with ease. In the petrous portions of both temporal bones large areas were replaced by soft, necrotic, bright yellowish nodules.

The thymus was normal in size and position but practically completely replaced by irregular, firm, yellow, discrete and confluent nodules.

The left lung weighed 100 Gm. and measured 13 by 9 by 4 cm. In the upper outer portion of the lower lobe a circumscribed nodule of caseous yellow material 1 cm. in diameter was found, encapsulated by dense connective tissue which sent linear projections into the surrounding pulmonary parenchyma especially in the direction of the regional lymph nodes. A similar but smaller and less sharply circumscribed lesion was present in the apex of the upper lobe. The remainder of this lung and the entire right lung, which weighed 130 Gm. and measured 14 by 9 by 4 cm., were red and mottled by grayish flecks.

Several bronchial lymph nodes were converted into dry caseous masses surrounded by dense fibrous tissue. Other thoracic and many abdominal nodes were enlarged, apparently hyperplastic, flecked with reddish spots and softened in areas.

The spleen, weighing 210 Gm. and measuring 13 by 7 by 4 cm., was moderately firm and on section presented a bright red pulp studded with sharply circumscribed, grayish dots resembling follicles.

The liver weighed 680 Gm. and measured 21 by 13 by 5 cm. The gallbladder and bile ducts appeared normal. In general the hepatic tissue was pale, friable and translucent. In the outer aspect of the left lobe there was a cystic area 2 cm. in diameter, filled with thin, opaque bile-stained fluid and lined on the inner aspect by a brown ragged membrane. The outer wall of this lesion consisted of a thick layer of dense fibrous tissue which sent prolongations into the surrounding parenchyma and contained several small, firm, yellow nodules.

The suprarenal glands were thin. The heart, pancreas, gastro-intestinal tract and genito-urinary tract showed no noteworthy changes.

Microscopic Examination: Lymph Nodes: The follicles were decreased in number and the lymph cords were atrophic with alterations in cellular content but without much change in structural pattern. There was marked diminution in the number of follicular and medullary lymphocytes with corresponding replacement by plasma cells, eosinophilic polymorphonuclear leukocytes and another type of cell which will be referred to hereafter as a "pleochromatic histiocyte." The last-mentioned type of cell was round, polyhedral, elongated or spindle-shaped, averaging 20 microns in diameter with frequent variations between 15 and 40 microns. The nucleus was pale, vesicular, centrally placed and sometimes crumpled, with a sharply etched outline dotted with small granules of chromatin. A dark, violet nucleolus was often observed. The cytoplasm was dense, dull, homogeneous, rarely slightly vacuolated and usually neutrophilic but with frequent variations toward acid or basic reactions. A few small black granules were frequently present in osmic acid preparations, and occasionally one or two reddish granules and needle-shaped crystals were observed after staining with nile blue sulphate. Many of the crystals were doubly refractile when viewed with crossed Nicol prisms. The pleochromatic histiocytes were present within and around lymph sinuses and blood vessels, in large numbers within the follicles, diffusely in areas of granulation tissue, and in rosette formations throughout the medulla. In association with other cells they formed an important constitu-

ent of nodular cellular collections which were most numerous in the medullary portions of the node and which were present also immediately beneath the capsule, where many of them occupied the positions formerly held by the follicles. As a rule these nodular lesions consisted exclusively of closely packed or discretely separated pleochromatic histiocytes, loosely supported by a delicate reticulum (fig. 1). Others contained eosinophils, lymphocytes, plasma cells, erythrocytes, pigment and strands of fibrin, all of which were subject to the phagocytic action of the pleochromatic histiocytes. Young vascular, edematous and hemorrhagic granulation tissue was interspersed around these nodules and elsewhere in the lymph node, distorting the architectural pattern somewhat and being

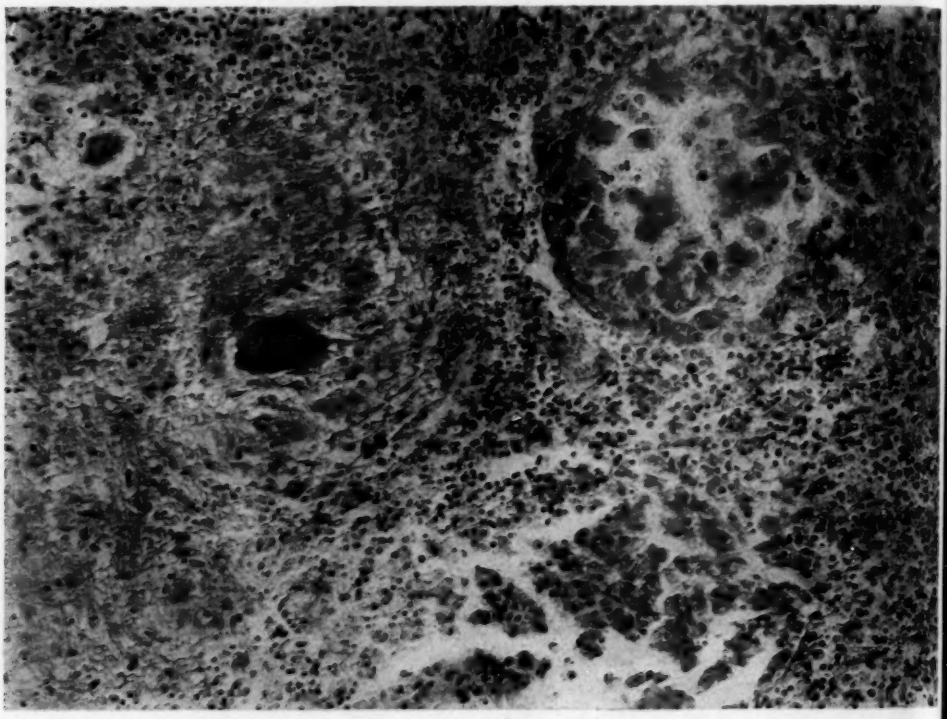


Fig. 1.—Bronchial lymph node showing two nodular cellular collections of xanthomatosis to the right and a small tubercle to the left. The nodule in the right upper part of the field is hemorrhagic and composed of loosely arranged pleochromatic histiocytes with engulfed pigment; reduced from × 200.

especially compact and hyalinized about the smaller blood vessels. Minute areas of hemorrhage were found in the lymph sinuses containing pleochromatic histiocytes and outside the capsule of the node. The picture in some of the bronchial lymph nodes was further complicated by the presence of tuberculous lesions in varying stages of activity (fig. 1). One such area measuring 3 by 6 mm. was composed of a central caseous and calcific mass encapsulated by dense hyalinized connective tissue directly continuous with an area of granulation tissue which contained focal collections of cells. Several discrete and small confluent miliary tubercles which sometimes involved the nodular cellular collections were

present in another node. Remnants of eosinophils and pleochromatic histiocytes were recognized in the central caseous area of some tubercles, which regularly showed a high lipin content.

Spleen: The appearance under crossed Nicol prisms, the reactions to fat stains and the other splenic changes were essentially similar to those in the non-tuberculous lymph nodes. However, there was a more marked tendency to the occurrence of peri-arterial fibrosis and hyalinization, and the replacement of lymphocytes by pleochromatic histiocytes appeared to proceed from the center of the follicle toward the periphery. The pleochromatic histiocytes were especially numerous in the red pulp about the borders of malpighian corpuscles where they occurred in rosette formation and in characteristic nodular cellular collections. Numerous small hemorrhages were scattered throughout the pulp, and accumulations of histiocytes, eosinophils, monocytes and lymphocytes were present beneath the intima of many of the larger veins.

Liver: The hepatic cells were separated by moderately dilated sinusoids and showed fine and coarse cytoplasmic vacuolation especially in the outer portions of the lobule. The Kupffer cells were large and numerous with abundant, vacuolated cytoplasm containing small granules of brown to olive green pigment. The portal radicles were prominent owing to an increased fibrosis and a marked infiltration of lymphocytes without much increase in the bile ducts. Under nile blue sulphate stain large and small globules of neutral fat were demonstrated in most of the hepatic cells in the extreme outer border of the lobule where many small dark blue granules were present in both the hepatic and the Kupffer cells. Many needle-shaped crystals arranged singly or in sheaves and staining various shades between red and blue were scattered throughout the lobule in the sinusoids, in the perivascular tissue spaces and in Kupffer cells.

The cystic area, noted grossly, was separated from the surrounding hepatic parenchyma by a thick, fibrous wall lined on its inner aspect by a wide zone of young granulation tissue covered by flattened, compressed cells on the surface and sparsely infiltrated by polymorphonuclear leukocytes, eosinophils, lymphocytes, monocytes, plasma cells and foam cells. The cytoplasm of the foam cell was usually abundant and appeared as a fine network of reticulated character containing varying quantities of amorphous granules or compact masses of pale or refractile yellow pigment. As a rule a single, small round nucleus dotted with finely granular chromatin material was present, but two or three nuclei were not unusual, and as many as fifteen were occasionally observed in the larger cytoplasmic masses. Red droplets of neutral fat and reddish granules, greenish needle-shaped crystals and coarse irregular red or blue spicules were demonstrated in the cytoplasm of these cells stained with nile blue sulphate. Under crossed Nicol prisms great numbers of doubly refractile needle-shaped crystals were observed. This layer of granulation tissue gradually became devoid of cells and was succeeded by a wide band of dense hyalinized connective tissue containing several larger arteries, veins, bile ducts and nerve trunks, but showing no tendency to infiltrate the hepatic parenchyma except for a few coarse prolongations.

Thymus: The thymus consisted principally of granulation tissue interspersed with linear and branching compressed streaks of lymphocytes, reticular cells and a few corpuscles of Hassall, composed of concentric rings of hyalinized or more or less calcific material, practically devoid of nuclei. The peripherally placed cells in these streaks frequently contained coarse droplets of neutral fat, reddish granules and greenish needle-shaped crystals in nile blue sulphate preparations.

The granulation tissue was very vascular and practically devoid of lipins in the immediate vicinity of the compressed thymic tissue where it was apparently youngest. Elsewhere the capillaries tended to disappear and the small blood channels remaining were rendered conspicuous by their thickened walls and perivascular hyalinization. Foam cells similar to those in the xanthomatous cyst of the liver were at times the only constituents of the granulation tissue and were also found in the adventitia of the vessels, in the perivascular fibrous tissue and outside the capsule of the organ (fig. 2). At other times lymphocytes, plasma cells, monocytes, eosinophils and many vacuolated histiocytes were scattered diffusely in the

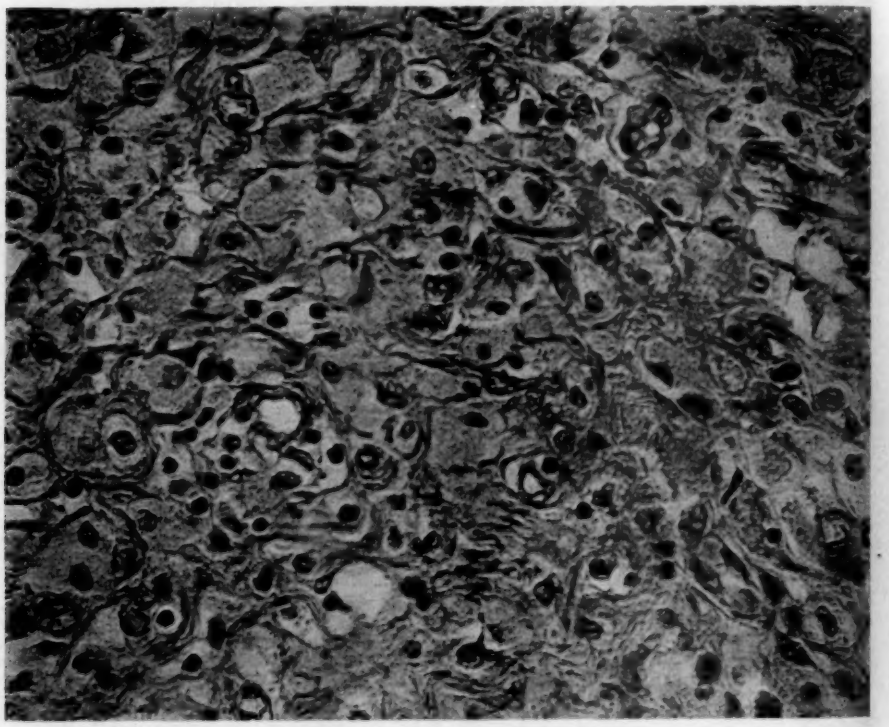


Fig. 2.—Section of the thymus showing a xanthomatous area of closely packed foam cells supported by connective tissue stroma; × 250.

meshes of the loose fibrillar reticulum. These cells also formed nodular cellular collections presenting a characteristic arrangement. The center was composed of monocytes, myelocytes and eosinophilic leukocytes densely packed together and surrounded in succession by (1) a narrow, clear border devoid of cells, (2) a cellular area containing extensively vacuolated pleochromatic histiocytes and several giant phagocytes supported by a loose fibrillar reticulum and (3) beyond this a syncytium of cells showing mitosis and mobilization. Transitional stages were observed between the foam cells and the pleochromatic histiocytes which became increasingly vacuolated. Round, refractile, acidophilic hyaline droplets were seen resembling those frequently observed in the renal tubular epithelium. Under crossed Nicol prisms great numbers of doubly refractile needle-shaped crystals were observed.

Lungs: The lumens of the alveoli and bronchi and the walls of the alveoli, bronchi and blood vessels contained varying numbers of lymphocytes, plasma cells, eosinophils, monocytes and especially pleochromatic histiocytes. Only an occasional foam cell was observed in the alveoli or lying against a septal wall. There were frequently a marked peribronchial and perivascular proliferation of granulation or hyalinized connective tissue which replaced large areas of pulmonary parenchyma, usually subpleural. These areas were studded with nodular cellular collections infiltrated by vacuolated histiocytes and surrounded by emphysematous pulmonary parenchyma. Old calcified tuberculous areas and discrete and small confluent miliary tubercles, similar to those in the lymph nodes, were also noted.

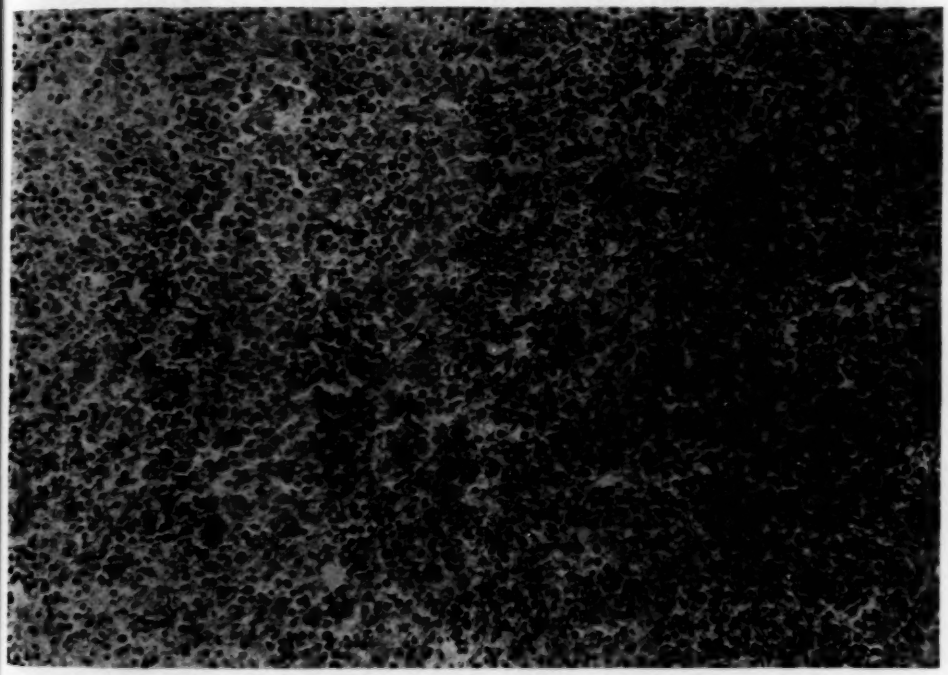


Fig. 3.—Bone marrow showing a gradual transition from hyperplastic marrow on the right to an area infiltrated by pleochromatic histiocytes which are difficult to distinguish from megakaryocytes; reduced from × 200.

Hypophysis: The nerve cells in the posterior lobe were reduced in number and separated, especially near the pars intermedia, by a slight diffuse and focal infiltration of lymphocytes, plasma cells, eosinophils, foam cells and single or multinucleated pleochromatic histiocytes supported by granulation tissue. The remainder of the hypophysis showed no noteworthy changes.

Dura: The outer surface (periosteal layer) was lined by a continuous layer of granulation tissue containing pleochromatic histiocytes, foam cells, lymphocytes, eosinophils and plasma cells scattered diffusely or arranged in nodular cellular collections. There was a tendency for the occurrence of perivascular hyalinization and fibrosis about several nerves and pacchionian bodies. Under crossed Nicol prisms there were great numbers of doubly refractile needle-shaped crystals.

Bone: The periosteal margin of the petrous portion of the temporal bone was partially decalcified and very irregular owing to small indentations occupied by osteoclasts. Along this line there were marked erosion and numerous spicules, small flecks and thin irregularly shaped segments of bone lying partially detached and sequestrated. The interior of the bone showed advanced destruction and partial replacement by granulation tissue similar to and continuous with that on the dura.

The outer periosteal fibers of the sternum split at certain points to encapsulate small round or flat nodules of granulation tissue containing numerous accumulations of foam cells. The bone underlying these nodules was atrophied. Similar nodules were present immediately inside the marrow cavity of some of the vertebral bodies.

Bone Marrow: The bone marrow of the vertebrae, sternum, ribs and femur showed marked hyperplasia of all the elements, especially of the eosinophilic myelocytes. The megakaryocytes were numerous and showed many degenerating forms. Scattered generally throughout the myeloid tissue, but especially in and about the nests of primitive erythrocytes, were many large single or multinucleated cells with an abundance of smooth, homogeneous, deeply staining, slightly acidophilic cytoplasm, resembling somewhat that of the megakaryocytes (fig. 3). When numerous these cells tended to displace the normal bone marrow elements. Other cells were present which resembled these in many respects except that the cytoplasm showed varying degrees of vacuolation. A section through the marrow of the femur showed a gradual transition between an area of hyperplastic myeloid tissue and an area of young granulation tissue, containing a few foci of marrow cells and many plasma cells, monocytes and large pleochromatic histiocytes. There was marked fibrosis about the larger blood vessels. Cells with hyaline droplets like those observed in the thymus were present in the bone marrow.

Kidney: There were marked vacuolation and swelling of the tubular epithelial cells and a slight cellular reaction with pleochromatic histiocytes in the connective tissue of the pelvis.

Suprarenal Glands: There was atrophy of the medulla and to a less extent of the cortex which showed marked lipoid depletion.

Brain: Significant changes were not present.

COMMENT

In this case the lesions did not present the lipoid reactions or the morphologic characteristics of Niemann-Pick's disease, and they can readily be distinguished from those of Gaucher's disease by the absence of the typical Gaucher cell with its clear, wrinkled and longitudinally striated cytoplasm. The essential features were manifestly those of Hand-Schüller-Christian's disease and included granulomatous lesions, hemorrhages, necroses, ultimate fibrous cicatricial transformation, dural and periosteal granulations, xanthomatous cysts of the liver, hypoplasia of the suprarenal glands and characteristic lesions in the lungs, kidney, bone marrow, thymus and pars nervosa of the pituitary gland. The foam cell was present in typical form in many areas and resembled that of the secondary xanthoma (Plewes [12]). The principal lesions, viewed under crossed Nicol prisms, contained many doubly refractile needle-

12. Plewes, L. W.: Arch. Path. **17**:177, 1934.

shaped crystals, and chemical analysis of tissue obtained from the dura, thymus and cyst in the liver showed a high content of cholesterol. In Cowie and Magee's [13] case the xanthomatous masses had a high content of total lipoid, 50 per cent of which was cholesterol. Hand-Schüller-Christian's disease is regarded as a disturbance of lipoid metabolism or of lipoid excretion resulting in the storage of lipoid substances in the granulomatous lesions of the various organs and tissues. There is phagocytic activity on the part of the cells of the reticulo-endothelial system which remove an excess of lipoids in certain areas in which infection or trauma, particularly of the bone and skin, may have stimulated a collection of histiocytes. Although infection has been shown to have some connection with the development of the disease, Sosman [7] emphasized the fact that it is frequently possible to obtain a history of preceding infection in the majority of diseases of childhood. Whether the disturbance in the lipoids and in the reticulo-endothelial system is due to an avidity of the cells for lipoids or is a compensatory mechanism resulting from a failure of proper fat metabolism is problematic.

The evolutionary type of process in Hand-Schüller-Christian's disease resembles that of lymphogranulomatosis, which occupies a borderline position between neoplasm and infection. These two conditions have been confused clinically and especially as the result of biopsy examination, but their manifestations are usually quite dissimilar, and the histologic pictures bear only a superficial resemblance to each other in atypical cases. Certain of the changes in the petrous portions of the temporal bones are suggestively similar to those of osteitis fibrosa cystica, a point stressed particularly by Snapper and Parisel.[14] Foot and Olcott [11] described a condition under the designation of nonlipoid histiocytosis in which the changes resembled those in the lymph nodes, spleen and parts of the bone marrow in our case. They collected from the literature a number of similar examples having in common this marked proliferation of lipoid-free histiocytes in association with eosinophils and plasma cells. Some of the cases were believed to be infectious in origin, others leukemic with aleukemic intervals, while those occurring in childhood regularly presented a marked generalized purpuric eruption of the skin and scattered small petechiae over the greater part of the body, leading to the diagnosis of thrombocytopenic purpura. The clinical picture was indefinite and poorly characterized, although a history of different types of recent infection was generally elicited and the changes in the lymph nodes were somewhat similar to those in nodes draining infected areas. It appears probable that a relationship may

13. Cowie, D. M., and Magee, M. C.: Arch. Int. Med. **53**:391, 1934.
14. Snapper, I., and Parisel, C.: Quart. J. Med. **2**:407, 1933.

exist between this group of so-called nonlipoid histiocytosis and at least some cases of Hand-Schüller-Christian's disease.

The marked overgrowth of pleochromatic histiocytes and the absence of foam cells in the lymph nodes, spleen and parts of the bone marrow are features of Hand-Schüller-Christian's disease which have not received general recognition. The cytoplasm of the pleochromatic histiocyte has been described as uniformly basophilic or eosinophilic with marked variations between these reactions (Robertson and Warren [15]). In our case it was usually basophilic in the lymph nodes, eosinophilic in the spleen and dura and pale and neutrophilic in the hypophysis; its other characteristics were quite uniform in the various organs and tissues in which it was studied. Its origin from the reticular cell of the splenic follicle was suggested by the fact that it appeared first in the center of the malpighian corpuscle. Some of its forms were difficult to distinguish from the megakaryocyte of the bone marrow and from bizarre types of multinucleated plasma cells in the spleen and lymph nodes. In the two latter situations only a small amount of lipoid material was stored in the pleochromatic histiocytes, although their phagocytic character was evidenced by the ingestion of pigment, débris and other cells. Transitional forms between these histiocytes and the foam cells in the dura, thymus, lungs and bone marrow were frequently encountered. The nodular cellular collections, composed of pleochromatic histiocytes alone or in association with other cells, represented a prevailing feature of all the granulomatous lesions of xanthomatosis. The foci composed exclusively of pleochromatic histiocytes had not been infiltrated by other cellular elements or the latter had undergone necrosis or been phagocytosed by the histiocytes. As the diffuse lesions of granulation tissue became less vascular and more compact and hyalinized with age, the walls of the remaining capillaries were thickened, and there were a perivascular deposition of dense collagen fibers and an infiltration of large single and multinucleated foam cells in certain situations, as in the thymus and dura.

The tuberculous foci in the lungs and lymph nodes were easily distinguished from the granulomatous lesions of xanthomatosis although there was a definite overlapping of the two in a few of the lymph nodes. In some instances miliary tubercles were engrafted secondarily on the nodular cellular areas, and remnants of pleochromatic histiocytes, eosinophilic leukocytes and plasma cells could be recognized in the caseous necrotic material. Frequently the pleochromatic histiocytes exhibited no apparent defensive reaction to the extension of the tuberculous process, but at other times they became radially arranged like epithelioid cells at the periphery of the tubercle; the cytoplasm tended

15. Robertson, S. H., and Warren, S.: Arch. Path. **15**:193, 1933.

to remain pleochromatic, and the nuclei became enlarged and more rectangular without undergoing mitosis. The areas of xanthomatous granulation tissue in the lung appeared to be especially susceptible to involvement by tuberculous lesions. In the case reported by Chiari [6] the patient died of cavernous pulmonary tuberculosis without xanthomatous involvement of the thoracic or abdominal viscera.

The morphologic changes in the thymus and suprarenal glands coupled with the emergency type of death occurring under ether anesthesia, which had, however, been administered successfully three times previously, emphasizes the operative risks involved when surgical procedures are contemplated in patients with Hand-Schüller-Christian's disease. In our case the heart and blood vessels were not particularly hypoplastic, but the suprarenal glands were small and thin and the structural alterations in the thymus were advanced. A definite statement cannot be made regarding a lowered alkaline reserve, but a single determination showed that the blood sugar was at a low normal level. There is not sufficient evidence at present to state that these features may constitute a new syndrome resembling that of status lymphaticus which has no very definite pathologic basis itself (Marine,[16] Young and Turnbull [17] and Waldbott [18]). The various syndromes, such as diabetes insipidus, infantilism, exophthalmos and others occurring in the group of lipoid diseases, apparently depend on the prevailing type of lesion involving different organs and structures of the body, being incidental and not essential features of the condition.

SUMMARY

A case is presented of lipoid granulomatosis (Hand-Schüller-Christian's disease) with widespread involvement of the organs and tissues and with coexistent tuberculous lesions in the lungs and lymph nodes. Death occurred suddenly under ether anesthesia.

16. Marine, D.: Arch. Path. **5**:661, 1928.
17. Young, M., and Turnbull, H. M.: J. Path. & Bact. **34**:213, 1931.
18. Waldbott, G. L.: Am. J. Dis. Child. **47**:41, 1934.

CARTILAGINOUS METAPLASIA IN AORTIC ATHEROSCLEROSIS IN A PARROT

R. D. Lillie, M.D., Washington, D. C.
Surgeon, United States Public Health Service

Fox [1] reports finding degenerative arterial disease in thirteen, or 1.8 per cent, of a series of birds of the order Psittaci. In his material medial degeneration and fibrosis of smaller vessels were more prominent, and the aorta was less often the principal site of the disease. Degenerative changes were more prominent than productive. Intimal proliferative plaques also occurred. Fox recorded no instance of cardiac hypertrophy or of myocardial scarring in Psittaci.

The bird which is the subject of this report was a large green female about 30 years old; it had been a household pet in one family for most of that time. It died with symptoms of diarrhea, and the carcass was sent to the National Institute of Health for examination as to the possible presence of psittacosis.

At autopsy the ascending and transverse aorta and the innominate artery were unusually thick and rigid, a change which extended to the subclavian arteries within the chest. The heart did not appear much enlarged, but was quite thick and muscular and was firmly contracted. Intestinal distention was the only other noteworthy gross observation.

Histologically the heart showed focal interstitial scars in the thickened musculature of the septum and left ventricle. The ascending and transverse aorta and the innominate artery presented a marked thickening of the intima irregularly encroaching on the musculo-elastic media. There were also a few focal interstitial fibrous scars in the markedly thinned media. The intima was basically fibrous. It contained a few focal areas of coarse vacuolation in which there were cellular necrosis and slight granular calcium deposition. There were also scattered clumps of needle-like clear spaces embedded in fibrous tissue, probably representing cholesterol crystals. The most striking change was the extensive replacement of the intima by irregular masses of typical hyaline cartilage. With the Giemsa stain the usual metachromasia of cartilage was present, but nonmetachromatic areas were often interspersed between the metachromatic pericorpuscular zones.

From the National Institute of Health.

1. Fox, Herbert: Disease in Captive Wild Mammals and Birds, Chicago, J. B. Lippincott Company, 1923.

Stains for fat showed large numbers of singly refractile globules staining intensely with sudan IV lying apparently in the cartilage cell spaces, and in the matrix, masses of doubly refractile material, part of which was tinged with sudan IV, lying in fibrous areas between the fibers. . Nile blue sulphate showed no fatty acids, but many of the globules in the cartilage were doubly refractile and divided into quadrants by a dark cross.

The descending thoracic aorta presented only an eccentric rarefied and vacuolated fibrous intimal plaque. The abdominal aorta, the pulmonary artery and its branches and the coronary, renal, splenic and hepatic arteries were normal. In accordance with the usual practice in presumably infected birds, the carcass was incinerated immediately after evisceration; hence, no material from the alar or femoral vessels was available.

SUMMARY

A case of atherosclerosis of the thoracic aorta in a parrot is reported. The sclerotic intima presented a minor amount of degenerative changes and an extensive cartilaginous metaplasia.

General Review

PATHOGENESIS OF POSTPRIMARY PROGRESSIVE TUBERCULOSIS OF THE LUNGS

R. H. JAFFÉ, M.D.
CHICAGO

For many years the interest of the pathologists was devoted to the changes of fully developed pulmonary tuberculosis, and many classifications were suggested which were based on the anatomic findings. Microscopic investigations disclosed the most minute details of the histogenesis, progression and regression of the specific reactions to the tubercle bacilli, and little additional information in these fields could be expected. At present the discussion of the pathologists centers about the point of origin of the progressive pulmonary tuberculosis of the postprimary period and about the rôle which exogenous superinfection and endogenous hematogenous infection of the lungs play in causing the isolated, progressive tuberculosis of this organ.

The studies of Birsch-Hirschfeld, von Baumgarten, Schmorl, Abrikosoff and Aschoff seemed to have so firmly established the apical beginning of pulmonary tuberculosis (phthisis pulmonum, Aschoff) that other possibilities received very little attention from the pathologists. The clinicians, however, were less unanimous in the assumption that progressive pulmonary tuberculosis always started in the apex. Fishberg stated that long before the use of x-rays two British authors, W. Ewart and J. Kingston Fowler, referred to the frequent subapical location of early tuberculous consolidations. With the introduction of roentgen rays in the diagnosis of pulmonary lesions the significance of the apical changes in tuberculosis became doubtful. According to Sweany, Cook and Kegerreis, Gekler was the first to champion the idea that roentgenologic findings pointed toward an infraclavicular location of the earliest lesions in pulmonary tuberculosis. Following the publications of Wessler and especially the fundamental studies of Assmann, numerous clinical and roentgenologic reports have established that progressive pulmonary tuberculosis most frequently starts acutely with a lesion below the clavicle.

From the Department of Pathology of the Cook County Hospital and the Uihlein Memorial Laboratory of the Grant Hospital.

The new conception of the great significance of the early infraclavicular infiltrations was bound to cause much concern among the orthodox believers in an apical beginning of pulmonary phthisis. To the morbid anatomists the findings of the roentgenologists were of limited value since the apical lesions might be so small as to require microscopic search. At a convention of specialists in tuberculosis in 1928, Graeff made the statement that there was no definite proof against the classic conception of the morbid anatomists that pulmonary tuberculosis, as a rule, started in the apex.

Fully developed pulmonary tuberculosis yields no information as to its probable point of origin. It may be recalled that judging the age of a tuberculous lesion from its morphologic appearance is often misleading. However, the incidental observations at autopsy of incipient pulmonary tuberculosis and its relation to preexistent and apparently silent foci are of the greatest significance for the study of the pathogenesis of pulmonary tuberculosis. In the present review it is intended to discuss the different tuberculous lesions which are encountered incidentally at autopsy as the remnants of the primary or of the postprimary infection from the standpoint of their phthisiogenetic potentialities.

THE APICAL LESIONS

For practical purposes the apex of the lung may be defined as the portion of the upper lobe which is bordered inferiorly by the clavicle. The anatomic apex is the extrathoracic portion of the upper lobe, located above the first rib. This portion is also called the vertex pulmonis (Anders). Provided the thorax is normal in shape the geometrically highest point of the lung in situ (culmen pulmonis) is found intrathoracically just below the tuberculum of the first rib (Anders). The straight apical bronchus supplies an oblique, cone-shaped area the base of which faces upward.

The apex of the lung, in particular its highest point, the culmen, is the most favored site of postprimary tuberculous processes. The explanations for the disposition of the apex to tuberculosis are many. Thus, it is often referred to the compression of the apex by the first rib, to the poor respiratory ventilation and to the sluggish circulation of the blood in this area. According to Orsos the pulling of the diaphragm acts most intensively on the apex since it is reduced to a small area causing foci of relaxation on the surface of the apex. In these foci of relaxation foreign material is apt to be deposited.

Though the postprimary tuberculous lesions are most commonly encountered in the apex, it is also in the apex that these lesions show the greatest tendency to heal. The disposition of the apex to tuberculosis, therefore, does not mean that progressive pulmonary tuberculosis

tends to start in the apex. In recent years one has learned to distinguish several types of apical lesions which seem to differ as to their phthisiogenetic potentialities.

Pleural Scars.—These scars, which occupy the posterior aspect of the apex in the region of the culmen or extend over the vertex in the form of a cap, are from one to several millimeters thick. They are often very firm, of cartilage-like consistency, and their outer surface may be smooth and shiny or fixed to the thoracic wall by fibrous bands. Microscopically they consist of the thickened visceral pleura and a subpleural layer of indurated and sclerosed lung tissue with small round cell infiltrations and an occasional glandular tubulus. Since there are often no definite histologic evidences of their tuberculous origin, several authors (Lubarsch, Schuermann, Oberndorfer) have questioned whether one is justified in considering all these scars as tuberculous. I believe, however, with Schmincke, Graeff, Anders, Loeschcke, Aschoff and Focke, that the great majority of them are the residues of abortive tuberculous infections. Wurm assumes that silicosis may lead to apical scars. However, the silicotic granulomas select chiefly the midportions of the lung. Nonspecific inflammations of the lung likewise do not gravitate to the apex. I do not have the impression that in influenza or pertussis (or measles) pneumonia the apexes of the lungs are particularly affected. Rubinstein emphasized that the purely fibrotic scars have no relation to progressing pulmonary tuberculosis.

Discrete Miliary Tuberculosis of the Apex (Miliaris Discreta, Neumann).—In young persons, especially in children below 15 years of age, one finds occasionally in the apex, just underneath the pleura, a group of pearly-gray nodules varying in size from that of a pinpoint to that of a pinhead, surrounded by normal or slightly congested lung tissue. In addition to these nodules the lung contains a well encapsulated or calcified primary lesion in some other area. On microscopic examination the nodules prove to be typical miliary tubercles chiefly of productive character (Huebschmann). There is a marked tendency to fibrotic involution, and the nodules become replaced by scar tissue, which under the influence of the emphysematous distention of the surrounding alveoli may be stretched so much that only a focal thickening of the stroma of the lung results. This focal interstitial fibrosis can be detected only by histologic examination. The small scars are of no significance as far as progression is concerned. In some instances, however, in which these scars are more marked, one may find a small bronchus or a bronchiolus the lumen of which contains a plug of inspissated caseous or caseocalcareous material, indicating that the lesions started to spread by aspiration. The dense scars may be visible on roentgen examination (fibrosa densa, Neumann).

The discrete miliary apical tuberculosis is undoubtedly hematogenous and may be described as an abortive early generalization restricted to the apexes (Huebschmann, Pagel, Neumann).

Simon's Foci.—Simon described in the lungs of children between 2 and 8 years of age symmetrical caseous nodules confined to the apexes. These nodules seem to develop immediately after the primary complex (subprimary) and are hematogenous, similar to the discrete apical miliary tuberculosis to which they are related (Huebschmann, Anders, Pagel). A characteristic feature of Simon's foci is their great tendency to calcification. In the early stages they are composed of confluent epithelioid cell tubercles with giant cells and central caseation. There is usually no perifocal exudation, and the bronchi are not involved (Anders). The tributary lymph nodes are found free from tuberculous changes. In spite of the limited activity which Simon's foci display, Pagel has expressed the opinion that in some instances they may lead to progression. Since the literature contains very few anatomic reports on Simon's foci, a personal observation may be described.

The case was that of a white girl, aged 5 years, who died of tuberculous leptomeningitis. At the medial aspect of the upper lobe of the right lung there was a well circumscribed, mortar-like primary lesion which measured 6 mm. in diameter. In the draining lymph nodes of that lobe calcified areas, some as large as 15 mm. in diameter, were found. Similar areas were present in the right epibronchial and paratracheal lymph nodes, while the lymph nodes at the left venous angle contained more recent caseous lesions. In the apex of each upper lobe an almost symmetrical, firm nodule was present. It measured 10:12:8 mm. in diameter and consisted of a dry caseous center surrounded by a thin, light gray capsule. About the nodule there were several yellow-gray areas varying up to 1 mm. in diameter which were embedded in moist and much congested lung tissue. The remaining portions of the lungs were free from changes.

Aschoff-Puhl's Foci.—Aschoff and his pupil Puhl have called attention to fibrocaseous nodules which occur in the apical and subapical parts of the upper pulmonary lobes and which increase in frequency with progressing age. The nodules are usually multiple and are considerably larger than the apical lesions described by Simon. Histologically one finds a caseous center surrounded by a thin, hyaline (Aschoff's specific) capsule and a thick, fibrotic (Aschoff's nonspecific) capsule. The latter is composed of atelectatic, indurated lung tissue rich in coal pigment and infiltrated by round cells. The caseous center may become calcified, but the calcification seldom is so marked that stony concretions are formed. Ossification is very rare. The tributary lymph nodes either are free from tuberculous changes or contain but a few abortive tubercles. According to Aschoff and Puhl, these histologic features are sufficiently characteristic to distinguish the apical nodules from the primary lesions, which have a thick specific and a thin

nonspecific capsule, tend to become ossified and are associated with marked tuberculous changes in the regional lymph nodes.

Aschoff is of the opinion that the nodules under discussion are due to an exogenous superinfection and are the most common source of the pulmonary phthisis. The majority of investigators agree with Aschoff that the apical nodules are postprimary, but with regard to the other points considerable disagreement of opinions exists. Pagel and Wurm have emphasized that the apical nodules are much too pleomorphic to be of uniform origin. Admitting that some of them are the result of an exogenous superinfection, they believe that the majority of them are hematogenous metastases. Aspiration from the primary lesion into the apex seems to be of little importance. The hematogenous infection of the apex may be part of an abortive early generalization in which the infection selects the disposed apical parts of the lung (Braeuning and Redeker). The Aschoff-Puhl foci then would be identical with the Simon foci, their larger size being due to an exacerbation of the originally small lesions. The hematogenous infection of the apexes may also occur in later life, e. g., from the exacerbation of a silent focus in a lymph node (Ghon's endoglandular exacerbation). Pagel's chief argument in favor of the hematogenous origin of the apical nodules is that he found them three times as often in generalized tuberculosis as in isolated pulmonary tuberculosis.

Birsch-Hirschfeld, Schmorl and Abrikosoff believed that the apical process started with a small tuberculous ulcer in the mucosa of a bronchus of the third to fifth order. Aschoff, Loeschcke and Graeff stress the intra-alveolar and interalveolar location of the earliest lesion with secondary spreading to the bronchi. The earliest stage, apparently, has not yet been seen. Schuermann, who made a most careful, systematic study of the first postprimary tuberculous changes of the lungs, stated that even in the earliest stages which he was able to observe both the bronchi and the respiratory parenchyma were found involved. There are exudative caseous and acinous productive foci arranged about a bronchus the mucosa of which is transformed into caseous material.

As far as the exact location of the nodules is concerned, Anders stated that in over 85 per cent of the cases the lesions select the territory of the dorsal, apical bronchus, i. e., the culmen. The farther away from the culmen, the less frequently is the lung tissue affected. Loeschcke, too, mentioned the region of the apical bronchus as the favorite site of the first postprimary tuberculous lesions of the lung. The ventral half of the apex is rarely affected (Zeiss). On the other hand, Schuermann summarized his findings as follows: About 60 per cent of the postprimary foci are located within from 3 to 4 cm. below the vertex. The rest of them are found at a lower level, sometimes

without any changes higher up. In general, the lesions at the lower level are larger and are related to larger bronchi than the lesions in the apex. They are also more apt to become transformed into small cavities. My own experience is fully in accord with that of Schuermann.

The apical caseous and caseocalcific nodules remain potentially active throughout life. They contain sometimes so many acid-fast bacilli that under low power magnification red areas are visible (Pagel). The progression may immediately follow the formation of the nodules, or the nodules may become well encapsulated and remain silent for a varying length of time, flaring up later. The continuous progression occurs chiefly in young persons. Schuermann gave the average age as 21.4 years. There are several routes for spreading. The infection creeps into adjacent alveoli and alveolar ducts, or the bacilli are carried by the blood and lymph stream into the surrounding lung tissue. The most important mode of progression, however, is by aspiration of infectious material from diseased bronchioli and bronchi into branches which come off from the same bronchus of the next higher order.

The exacerbation of foci at first silent is much more common than the direct continuation (Schuermann). It is a phenomenon of later life. In twenty-eight cases which Schuermann studied, the patients' ages varied between 24 and 76, with an average of 53. The indurative processes about the caseous nodules often lead to pleural retraction, to emphysematous distention of adjacent areas and to small bronchiectases (Pagel and others). The caseous or chalky centers of the nodules are apt to become liquefied or sequestrated. At autopsy one finds occasionally in the midst of the dense and anthracotic tissue a small cavity which contains a moderately firm calcium concretion or a pasty, light gray material. Microscopically the pasty material consists of fatty débris, cholesterol crystals and elastic fibers, and eventually also of calcium granules. Tubercle bacilli can be easily demonstrated by direct smears, culture or animal inoculation. After removing the content the cavity presents a smooth, light gray inner lining. If a sequestrated or liquefied nodule breaks into one of the emphysematous blebs or bronchiectases previously described the way to aspiration and progression is opened. Some of the content of the small cavities may be expectorated, and after a severe attack of coughing the patient detects the peculiar looking material in his sputum. The demonstration of fragments of elastic fibers and of tubercle bacilli distinguishes this material from the nonspecific concretions which occasionally form in the lumens of bronchi.

Stefko attributes much significance to "alterative cavities" which may form about the nodules, leading to their sequestration. According to this author these parafocal or perifocal alterative cavities result

from a liquefaction of the lung tissue about the nodules which is due to a suddenly developing negative allergy, to a "breaking down of the symbiotic immunologic relation between host and micro-organisms." Another mode of exacerbation, finally, consists of the gradual transformation of the nonspecific capsule into tuberculous granulation tissue.

The causes which lead to the flaring up of the silent lesions are difficult to determine. Stefko's explanation is purely theoretical. Autopsy observations show that this flaring up is most commonly encountered in patients with diabetes mellitus, in pregnant women and in people who died of chronic wasting diseases, especially malignant tumors. Exogenous superinfection may stimulate the old foci to new activity by means of a tuberculin-like action of the newly inhaled tubercle bacilli on the preexistent lesion. Nontuberculous changes about the encapsulated nodules may favor their progression. This is illustrated by the following case:

A white woman, 41 years of age, died of an ulcerated carcinoma of the rectum with extensive metastases to the liver. In the upper third of the upper lobe of the right lung there was a single metastasis which measured 16 mm. in diameter and compressed the proximal portion of the subapical bronchus. Distal to the compression the bronchus was dilated and filled with thick, creamy pus. The lining of the bronchus was transformed into caseous material. The dilated bronchus terminated in a subpleural fibrocaseous nodule which measured 15 mm. in diameter and was partially liquefied. About the apical, subapical and horizontal bronchi there were multiple small foci of exudative caseation. I believe that in this case the exacerbation and acinous spreading of the subapical lesions were stimulated by the compression of the subapical bronchus by the metastasis. The tumor cachexia may have contributed to the exacerbation, but a nodule in the apex of the upper lobe of the left lung showed no signs of activity.

A critical analysis of the potentialities of the apical lesions on the basis of pathologico-anatomic observations leads to the conclusion that the caseous and caseocalcific nodules may cause dissemination. This dissemination, however, is usually limited and of small caliber. Are there any indications that the apical lesions may indirectly become the source of progressive phthisis by way of the infraclavicular infiltration?

THE INFRACLAVICULAR INFILTRATIONS

In the literature on tuberculosis the term infiltration is usually applied to lesions which are marked by their lability. These infiltrations may form and disappear quickly and may leave no roentgenologically demonstrable residue. On the other hand, they often show rapid caseation, liquefaction and ulceration followed by massive bronchogenic spreading. Though the infiltrations show a predilection for the infraclavicular region they may affect any portion of the lung. They are not specific of a certain stage of the tuberculous disease in the sense of

Ranke, since they may develop secondarily about primary lesions, about their lymph node component, about lesions of the generalization period and in incipient, isolated, progressive pulmonary tuberculosis. Some cases of epituberculosis are apparently due to an extensive perifocal infiltration about caseous foci in the hilus lymph nodes.

About the pathology of the transient infiltrations and the earliest stages of the caseous and ulcerative infiltrations little is known. There are very few reports (Assmann, Elias, Kudlich and Reimann, Loeschcke, Mischkowsky, Pagel, Rubinstein, Schmincke, Schuermann), and the majority of these reports deal with rather advanced changes. It is likely that the majority of the transient infiltrations are purely exudative processes which do not reach the stage of caseation. Pagel spoke of a viscid, plasmatic exudate in the alveoli, rich in mononuclear alveolar phagocytes. The alveolar septums are thickened and infiltrated and contain an occasional giant cell or abortive miliary epithelioid cell tubercle. Thus, the picture resembles a gelatinous pneumonia. In other instances, circulatory processes in the form of prestasis, stasis and hemorrhage predominate (Schuermann). These lesions are capable of complete resorption. Delay of the resorption may be due to fibrosis of the alveolar septums, collapse induration and nonspecific organization of the alveolar exudate.

Some of the transient infiltrations center about small caseous nuclei (Assmann). They are then perifocal reactions in a highly sensitive person (Ranke, Tendeloo). After resorption of the perifocal exudate the remaining caseous area may be too small to be visible on x-ray examination. The caseous area may become gradually replaced by connective tissue and the emphysematous distention of the surrounding alveoli may stretch the scar, making it fit into the framework of the adjacent lung parenchyma. There is then an almost complete restitutio ad integrum.

When the infiltrations take a turn for the worse the exudation is followed by caseation. The caseous material becomes liquefied; it finds its way into a bronchus, and a cavity is formed. The cavities which develop from the liquefied infiltrations are characteristic. They are usually spherical and possess a thin wall the inner lining of which is smooth. After the perifocal reaction has subsided the cavities are surrounded by practically normal lung tissue. These "punched-out" cavities differ in many respects from the cavities of chronic ulcerative tuberculosis, which are surrounded by a thick, sclerotic wall the inside of which is covered by a layer of caseous material. The rapid liquefaction of the caseated infiltration is very dangerous, since it opens blood vessels and bronchi. Hemorrhage and aspiration result, and the infection spreads rapidly to other portions of the lung.

The infraclavicular infiltrations do not lead to specific changes in the regional lymph nodes. If tuberculous changes are present, they are, as a rule, older than the process in the lung (Pagel, Schmincke, Schuermann, Loeschcke, Beitzke).

The different pathologico-anatomic manifestations of the tuberculous infection have often been linked to immunity and allergy and Ranke especially suggested a geneal classification of tuberculosis on the basis of immunologic and allergic phenomena. Ranke's conception has often been interpreted wrongly, and there is so much discrepancy in the modern literature that it has become somewhat discredited to speak of immunity and allergy in tuberculosis. The critical observer, however, cannot help feeling that the infraclavicular infiltrations, with their massive exudation and quick liquefaction, carry the earmarks of an allergic, in particular hyperergic, inflammation. They are the response of a sensitized organism. In this connection, it may be recalled that allergy and immunity are not related (Rich) and that hyperergic inflammation does not indicate increased protection.

THE RELATIONS BETWEEN THE INFRACLAVICULAR INFILTRATIONS AND THE APICAL LESIONS

Loeschcke and Huebschmann maintain that the infraclavicular infiltrations are always secondary to apical lesions. A similar opinion is held by Aschoff and Graeff. In the preceding section I described a caseous inflammation of the bronchioli and finest bronchi which is found in connection with the apical caseous nodules. Aspiration of infectious material from the finest bronchi may cause the tuberculosis to spread to other branches of the dorsal apical bronchus, and minute aspiration foci are formed, which are chiefly productive. These minute foci have a tendency to heal, but the process may slowly spread in the craniocaudal direction (small shotlike dissemination of Loeschcke).

By direct continuation or following an exacerbation the caseous endobronchitis may descend into larger branches until it reaches the main apical bronchus, the lumen of which becomes filled by a cast of caseous material. Loeschcke stated that the infraclavicular infiltrations result from the massive aspiration of tuberculous material into the subapical and horizontal bronchi. The massive aspiration causes exudative inflammation with caseation and ulceration (coarse shotlike dissemination). Loeschcke's interpretation has been confirmed by Schuermann, Pagel and Aschoff, and I have repeatedly been able to trace an infraclavicular caseous or ulcerative process to an older focus in the apex. Loeschcke's explanation, however, does not take into account the transient infiltrations, which, though extensive, may become completely resorbed. Schuermann stressed the fact that coarse shotlike dissemination is not

always bound to the caseous inflammation of a larger bronchus. It may also follow small initial lesions when many bacteria of great virulence are aspirated.

In addition to the aspiration from the apex into the infraclavicular region there occur infraclavicular infiltrations which are not related to apical lesions. In these cases, either the apex contains only silent and completely encapsulated nodules or fibrotic scars or it is free from changes and the infraclavicular infiltration is the first manifestation of the postprimary pulmonary tuberculosis (Elias, Kudlich and Reimann, Mischkowsky, Pagel, Schuermann, and others).

The acute formation of an infraclavicular cavity without apical lesions is illustrated by the following case:

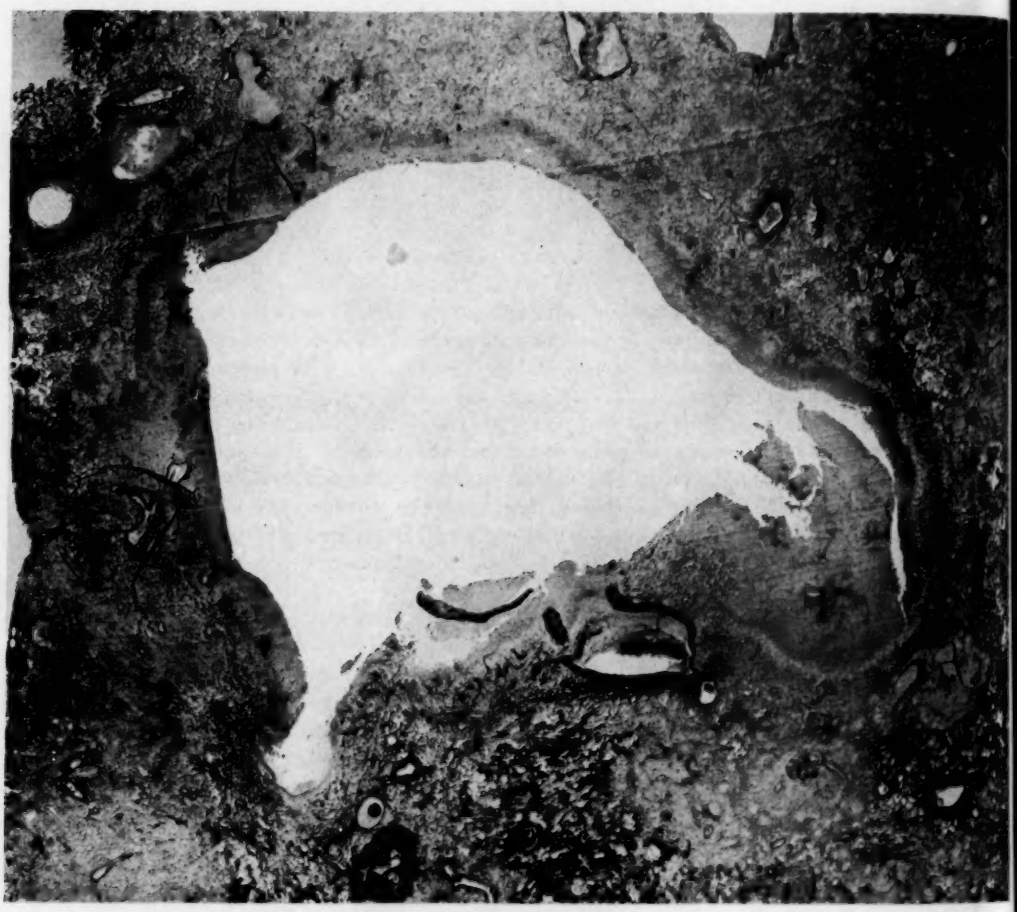
A colored man, aged 38, stated that he was perfectly well until five weeks before his admission to the hospital, when he experienced a sudden chill with severe headache which was followed by fever and cough productive of a mucoid material. During the last three weeks prior to admission he lost 5 pounds (2.3 Kg.) in weight and was in bed most of the time. There was no history of tuberculosis in his family. On admission his temperature was 102.4 F. The respiratory rate was 28, and the pulse rate, 112. There was diminished resonance over the entire left lung and an area of dulness was noted between the left clavicle and the nipple. Over this area amphoric bronchial breathing and bubbling râles were heard. Roentgen examination revealed clear apexes and an opacity in the middle third of the left lung. The sputum contained many tubercle bacilli. The blood count showed hemoglobin, 80 per cent; erythrocytes, 4,200,000, and leukocytes, 4,400. After a stay of a few days in the hospital the patient suddenly became very dyspneic and died.

At autopsy the left lung was distended and heavy, and multiple small areas of consolidation were felt in the lower two thirds of the upper lobe and in the upper third of the lower lobe. At the border between the upper and the middle third of the upper lobe there was a sharply circumscribed, roughly spherical cavity which measured 23 mm. in diameter and was filled with blood. The cavity was lined by a friable, light yellow-gray membrane and was surrounded by confluent, opaque, light yellow areas which averaged 10 mm. in diameter. These areas extended throughout the lower half of the upper lobe and the upper half of the lower lobe. The lung tissue about the areas was deep purple-red and very moist. The bronchi contained bloody mucoid material. The lymph nodes at the hilus were small, firm and anthracotic. The right lung contained air, and there were small areas of aspirated blood in the lower lobe. The apexes of both lungs were free from scars or fibrocaseous nodules. Near the base of the lower lobe of the right lung there was a subpleural calcified nodule the size of a cherry stone.

On microscopic examination no tuberculous lesions or scars could be detected in the apexes. The cavity was lined by a layer of caseous material which contained an enormous number of acid-fast bacilli. The caseous material rested on a very thin membrane which was densely infiltrated by small round cells and contained only a few Van Gieson red fibrils. There were many congested capillaries. The cavity communicated with two small bronchi the mucosa of which had been replaced by caseous material. The larger of the two bronchi had a diameter of 4 mm., and

the accompanying artery opened into the cavity (see illustration). About the cavity there were many foci of a caseating exudation with numerous tubercle bacilli and an intense perifocal reaction.

While in this case the cavity was in an early stage of formation the next observation is an example of a typical "punched-out" cavity.



An early infraclavicular cavity. Note the eroded artery in the lower wall of the cavity and the extension of the caseation into the adjacent bronchus, the marked perifocal reaction about the cavity and the foci of exudative caseation. Weigert's elastin stain; magnification, × 5.

The patient, a white woman 45 years of age, was brought to the hospital in coma and died four hours later. The autopsy revealed chronic meningo-encephalitis with severe acute degenerative changes of the ganglion cells. On the lateral aspect of the upper lobe of the left lung, at the border between the upper and the middle third, there was a firm subpleural area from 2 to 3 cm. in diameter. Sectioning

this area exposed several dry, caseous foci from 1 to 6 mm. in diameter which were located posteriorly to a spherical cavity 18 mm. in diameter. The cavity was lined by a thin, light purple-gray membrane the inside of which appeared smooth. The bronchi of this region were dilated and filled with a mucopurulent material. The apex was adherent to the wall of the chest and contained a small anthracotic scar. The apical bronchus was free from changes, as were also its tributaries. The hilus lymph nodes were small and deeply anthracotic. Microscopically the dry areas proved to be foci of caseous bronchopneumonia with a moderate perifocal reaction. The lining of the cavity was formed by Van Gieson's red connective tissue. There was no caseous material on the inside of this membrane, and the lung tissue about the cavity was not indurated.

In some instances the apex and the subapical region are found diffusely involved and the process is so uniform in character that one is justified in assuming a simultaneous involvement of both parts. Even serial sections fail to disclose an old focus. A case of this type may be briefly described.

A white man, aged 49, died as a result of fatty necrosis of the pancreas with diffuse serofibrinous peritonitis. The right lung was covered by a loosely adherent, soft membrane of fibrin. The upper fourth of the upper lobe felt firm, while the remaining portions were crepitant. On the sectioned surface the firm area was uniformly granular, dry and pale yellow. The apical and subapical bronchi were completely obscured by this area, as was also the distal part of the horizontal bronchus. In the lower portion of the upper lobe of the right lung and in the posterior part of the lower lobe of each lung there were several dry, yellow-gray areas, varying in size up to that of a pinhead. On the anterior aspect of the upper lobe of the left lung, near the lower border, there was a fibrocalcareous primary lesion which measured 10 mm. in diameter. The lymph nodes at the hilus of each lung were small and contained a few fibrocalcareous nodules. Microscopic examination of the consolidated area of the upper lobe of the right lung showed diffuse caseation of the alveolar walls and alveolar exudate with preservation of the elastic fibers. There were no epithelioid cell tubercles or giant cells nor any older changes.

Finally, it may be mentioned that apical lesions may be caused by aspiration from the infraclavicular process.

THE PATHOGENESIS OF THE INFRACLAVICULAR INFILTRATIONS

In a recent publication, Terplan reported that he had found in Buffalo a relatively small percentage of primary lesions in children and young adults. After the age of 20 years the pulmonary primary lesions increased in frequency. The author discusses the possibility that primary infection may also occur after the second and third decades of life. My experience in Chicago has been similar to that of Terplan, namely, after the age of 30 years residues of the primary infection are more common than below this age. Kalbfleisch observed typical recent pulmonary primary lesions in old persons and assumed that in these instances the effect of the primary infection acquired in early life had

completely subsided. The question will therefore arise whether a primary lesion with a marked perifocal reaction may present itself under the picture of an early infraclavicular infiltration. There are, however, principal differences between a primary lesion and an infraclavicular infiltration. The primary lesion is characterized by its stability and by its tendency to become encapsulated. The infraclavicular infiltration is labile. It may clear up completely or may rapidly progress to ulceration and cavitation. The primary lesion is followed by marked caseous tuberculosis of the tributary lymph nodes, while the infraclavicular infiltration does not spread to the lymph nodes. It is, however, possible that a primary lesion may cause an infraclavicular infiltration by aspiration. Mischkowsky described the case of a girl, aged 19, in which autopsy revealed a caseous and ulcerated infiltration in the infraclavicular region of the right lung which he thought was due to a bronchogenic dissemination from an exacerbating primary lesion in the upper lobe of the left lung

When Assmann published his first observations on infraclavicular infiltrations he came to the conclusion that they were the result of a postprimary exogenous superinfection. Many authors have accepted Assmann's point of view, stressing that the infiltrations are most commonly found in people known to have been exposed, such as physicians, nurses and autopsy helpers. It is, however, likely that these people are more apt to come under early observation than persons with other occupations. Kudlich and Reimann came to the conclusion that in their case exogenous superinfection offered the best explanation. Their explanation has not been accepted by Pagel. In the case of early infraclavicular cavitation which I have described here there were no evidences of an exacerbating pulmonary or extrapulmonary focus which may have served as a source of the recent process. Pagel, too, has admitted that some of the infraclavicular infiltrations may result from a new, exogenous infection with tubercle bacilli (see also Loeschcke, Schuermann, Aschoff and Graeff).

Adler, Albert, Braeuning and Redeker, Lydtin, Ulrici and others have offered clinical and roentgenologic evidences that hematogenous foci may progress to form early infraclavicular infiltrations and pulmonary phthisis. Pagel emphasized that in generalized forms of tuberculosis which are due to a prolonged dissemination of tubercle bacilli through the blood stream punched-out cavities in the infraclavicular region are encountered which are identical with the cavities that develop from early infiltrations (see also Schuermann and Pinner). In generalized tuberculosis the lesions tend to become stabilized, and massive bronchogenic spreading is relatively rare. There is a certain antagonism between generalization and local progression. In some instances,

however, the metastases are confined to the lungs and select the infraclavicular region. At first the hematogenous metastases become encapsulated and even calcified. As in the case of the apical lesions previously described, exogenous superinfection or decrease in resistance may cause a flaring up and progression of the isolated infraclavicular foci. The source of the hematogenous foci can be found in an active process in the lymph nodes or in tuberculosis of the bones, joints, genito-urinary tract, etc.

Liebermeister spoke of tuberculous hemorrhagic infarcts of the lung which may give a roentgenologic picture similar to that of an infraclavicular infiltration. In one of his cases he described a wedge-shaped hemorrhagic area which extended from the hilus through the lower part of the upper lobe. At the hilus a cherry-sized caseated lymph node was present, and there was severe tuberculous involvement of the blood vessels. Similar lesions were mentioned by Graeff and Küpferle and by Tendeloo. In this connection the "round tuberculous foci" may be discussed.

The Round Tuberculous Foci.—Albert has called attention to round tuberculous foci of the lung which are usually discovered incidentally on roentgen examination of the chest. These foci do not cause any symptoms. The patient is afebrile, the sputum is free from tubercle bacilli and the sedimentation rate of the erythrocytes is not increased. Because they are so sharply defined the round foci resemble metastases of a tumor. They have also been confused with cysticercosis (Jacksch von Wartenhorst). The foci are single or multiple, and as many as fourteen have been counted in a single case. They occur in any part of the lung but are most common in the infraclavicular region.

The round tuberculous foci often remain stationary for many months or even for several years. This inactivity distinguishes them from the infraclavicular infiltrations. Their ultimate fate varies. Bruck observed multiple foci in the lung of a woman, 32 years of age, which disappeared spontaneously. Some of the foci become calcified, while others are gradually replaced by connective tissue and transformed into scars. Albert and Straub emphasized that the prognosis is not always favorable. After a period of inactivity the foci may start to progress or they may break down and form a cavity with the danger of aspiration. Their relation to the infraclavicular infiltrations is still under discussion. Pagel, among others, believes that they may become the starting point of pulmonary phthisis. The symmetrical location in both lungs suggested to Albert a hematogenous origin.

Anatomically the round foci are purely exudative and caseous (Albert, Lachmann). The lymph nodes are usually not involved. Anders observed a patient with caseation in the regional lymph nodes

and considered the lesion as due to a primary infection. Lachmann isolated bovine tubercle bacilli, while Albert obtained a strain of human tubercle bacilli. Since very few anatomic reports have been published, a typical case may be described. Unfortunately, no roentgen picture was made during the patient's brief stay in the hospital.

A white woman, 36 years of age, died after a stay in the hospital of twenty hours. The clinical picture was dominated by severe vaginal bleeding which led to a provisional diagnosis of incomplete abortion. At autopsy a fibrocaseous primary lesion 10 mm. in diameter was found in the middle lobe of the right lung. The lymph nodes at the hilus of the right lung contained several dry, cheesy nodules which were surrounded by a thick fibrous capsule. In some of the nodules the capsule was partially destroyed, and groups of confluent tubercles with central caseation were found about the older lesions. The paratracheal, bifurcation, peribiliary, peripancreatic and periaortic lymph nodes were the sites of numerous, confluent, soft, caseous areas which varied from 25 to 40 mm. in diameter. There was a bilateral caseosuppurative salpingitis, as well as a discrete miliary dissemination to the spleen, liver and kidneys and a terminal endocarditis of the mitral valve. The endometrium was pale and smooth.

In the subapical portion of the upper lobe of the left lung there were two sharply circumscribed flat, round nodes, 15 and 17 mm. in diameter. They were firm and were composed of a homogeneous light yellow-gray material. In the subapical portion of the upper lobe of the right lung a single similar node 18 mm. in diameter was found. Histologic examination of the nodes showed diffuse caseous pneumonia. In sections stained for elastin the elastic fibers of the alveoli, bronchi and blood vessels were seen to be well preserved. About the caseous area there was a narrow zone in which the alveoli contained a fibrinocellular exudate. Tubercle bacilli could not be demonstrated.

I believe that this case proves the hematogenous origin of the round foci. The source of the hematogenous dissemination was found in the progressive tuberculosis of the lymph nodes which followed the endoglandular exacerbation of older lesions in the hilar lymph nodes. The foci in the lungs and those of the tuberculous salpingitis were of about the same age. In addition to these older hematogenous seedlings there was a recent miliary dissemination.

Summary.—The present knowledge of the pathology and pathogenesis of the infraclavicular infiltrations can be summarized as follows: Pathologico-anatomic observations confirm the clinical conception of the great significance of acute exudative infraclavicular processes as the source of progressive pulmonary tuberculosis. In the majority of the cases these infraclavicular processes reveal relations to older apical lesions. Thus they form the bridge between apical tuberculosis and pulmonary phthisis. In some instances, the infraclavicular infiltrations develop independently of or without apical foci. Clinicians give the incidence of the apical beginning of pulmonary tuberculosis as from 2.6 to 7.6 per cent (Braeuning and Redeker, Lydtin, Kayser-Petersen, Edel and Adler, Rubinstein). From the standpoint of the morbid

anatomist these figures are undoubtedly too low. Because of the scarcity of suitable material exact pathologic data are not yet available. Hematogenous infection of the lung is apt to produce the clinical and anatomic picture of infraclavicular infiltration and cavitation. There are, however, a considerable number of cases which strongly suggest that infraclavicular infiltrations may also develop from exogenous superinfection.

THE PRIMARY COMPLEX

The Pulmonary Primary Lesion.—The relation between the pulmonary primary lesions and the infraclavicular infiltrations has been discussed in the preceding section. In general, the primary lesions do not play an important rôle in causing isolated progressive pulmonary tuberculosis. Blumenberg assumes that in adults the primary infection of the lung does not take the typical course with encapsulation and caseation of the regional lymph nodes but rather tends to direct progression. Pagel and Beitzke do not agree with Blumenberg, and according to Pagel, Schuermann, Kalbfleisch, Terplan and many others the primary lesions contracted after adolescence are identical with those acquired in early life.

Exacerbation of an encapsulated primary lesion of the lung has often been described. In the literature reference is made to transient infiltrations about primary lesions, to extracapsular tubercle formation and to ulceration and sequestration of primary lesions (Pagel, Beitzke, Ghon, Schmincke and others). In a man 24 years of age who had committed suicide Wurm found a calcified primary lesion of the lung which was surrounded by recent tuberculous changes. The same author described, in a boy, 14 years of age, an ulcerated primary lesion of the lung (Schmincke's primary cavity type b) with massive bronchogenic dissemination. The majority of the exacerbating primary lesions, however, do not progress. The transient infiltrations are resorbed without leaving any traces and the extracapsular tubercles become fibrosed. Stefko referred to alterative cavities about the primary lesions which cause sequestration of the lesions. These sequestrated primary lesions are usually expectorated.

Siegen described a vascular pedicle through which the primary lesion is connected with the surrounding lung tissue. This pedicle offers a pathway to the tubercle bacilli in the center of the lesion. The significance of the vascular pedicle has been questioned by Pagel. It has not been definitely established how long viable tubercle bacilli persist in calcified and petrified primary lesions. At present the majority of investigators believe that the infectiousness of the primary lesions decreases markedly with progressing age. Sweany made the statement that he had not been able to decide whether the regressive changes

which cause the destruction of the wall of the primary lesions may lead to a liberation of latent bacilli. He considers it possible that nature may defeat her own purpose by opening the way to progression of the infection. I believe that the ossification which so often takes place in older primary lesions indicates absence of tubercle bacilli from the calcified center. This ossification is initiated by the ingrowth of young granulation tissue which is derived from the capsule. If viable tubercle bacilli were present in the calcified material which is destroyed and replaced by the granulation tissue, tubercles would be formed as a specific reaction to the surviving bacilli. In a large series of primary lesions in various stages of ossification I have not encountered a single instance of tubercle formation by the young granulation tissue. I believe that the persistence of tubercle bacilli in the Aschoff-Puhl foci interferes with the ossification of these lesions.

The Lymph Node Component.—In the lymph node component of the primary lesions exacerbation is undoubtedly more common than in the primary lesion itself. The significance of this endoglandular exacerbation for the hematogenous infection of the lung has already been referred to. The majority of authors assume that retrograde lymphatic spreading from an exacerbated focus in a hilar lymph node into the lung is rare. Wurm observed the perforation of an exacerbated lymph node tubercle into a large bronchus with aspiration.

THE REMNANTS OF EARLY GENERALIZATION

The primary tuberculous infection is apt to lead to an invasion of the blood stream. In the severe form this early generalization causes the acute miliary tuberculosis which immediately follows the primary complex and shows a high incidence of involvement of the meninges. In the great majority of the cases sufficient resistance has developed during the formation of the primary complex to check the invasion of the blood stream, and no colonization or an abortive colonization takes place in the different organs. This abortive generalization escapes clinical detection. The small hyaline or calcified nodules which are sometimes found at autopsy in the spleen, lungs, liver, kidneys and other organs are the remnants of the checked early generalization. It is from the isolated hematogenous foci that progressive tuberculosis of the bones, joints, kidneys, tubes, etc., takes its origin (Ranke). As far as the lungs are concerned the hematogenous foci may be confined to the apexes (Simon's foci and perhaps also some of the Aschoff-Puhl foci). They may also be found scattered throughout the lungs, and if they are of sufficient size and densely calcified, they may be visible on roentgen examination and may be mistaken for multiple primary lesions.

Schmincke expressed the opinion that any of the pulmonary nodules may flare up and lead to progressive tuberculosis. Wurm, a pupil of Schmincke. compared the frequency of the calcified nodules in tuberculous and nontuberculous lungs and found a much higher incidence in the former. There were also microscopic evidences of exacerbation and progression.

BIBLIOGRAPHY

Abrikosoff: Virchows Arch. f. path. Anat. **178**:173, 1904.

Adler, H.: Beitr. z. Klin. d. Tuberk. **80**:22, 1932.

Albert, A.: Beitr. z. Klin. d. Tuberk. **78**:647, 1931.

Anders, H. E.: Verhandl. d. deutsch. path. Gesellsch. **24**:186, 1929; Med. Klin. **29**:777, 1933.

Aschoff, L.: Klin. Wchnschr. **8**:1, 1929.

Ueber die natuerlichen Heilungsvorgaenge bei der Lungenphthise, Munich, J. F. Bergmann, 1921.

Assmann, H.: Beitr. z. klin. d. Tuberk. **60**:526, 1923; Med. Klin. **28**:1335, 1932.

von Baumgarten, P.: Beitr. z. path. Anat. u. z. allg. Path. **69**:27, 1921.

Beitzke, H.: Beitr. z. Klin. d. Tuberk. **65**:291, 1926.

Birsch-Hirschfeld, F. H.: Deutsches Arch. f. klin. Med. **64**:58, 1894.

Blumenberg, W.: Klin. Wchnschr. **8**:505, 1929.

Braeuning, H., and Redeker, F.: Studien zur Entwicklung der menschlichen Lungenphthise: I. Die hämatogene Lungentuberkulose des Erwachsenen, Leipzig, Johann Ambrosius Barth, 1931.

Bruck, S.: Am. J. Roentgenol. **31**:319, 1934.

Elias, B.: Beitr. z. Klin. d. Tuberk. **80**:175, 1932.

Fishberg, M.: Pulmonary Tuberculosis, ed. 4, Philadelphia, Lea & Febiger, 1932.

Focke: Beitr. z. Klin. d. Tuberk. **59**:228, 1924.

Gekler: Arch. Int. Med. **20**:32, 1917.

Ghon, A.: Ztschr. f. d. ges. exper. Med. **50**:25, 1926.

——and Kudlich, H.: Die Eintrittspforten der Infektion vom Standpunkt der pathologischen Anatomie, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930.

Graeff, S.: Beitr. z. Klin. d. Tuberk. **70**:173, 1928.

——and Küpferle, L.: Die Lungenphthise, Berlin, Julius Springer, 1923.

Huebschmann, P.: Pathologische Anatomie der Lungentuberkulose, Berlin, Julius Springer, 1928.

Kalbfleisch, H. H.: Ergebn. d. ges. Tuberk. **4**:47, 1932.

Kudlich, H., and Reimann, F.: Ztschr. f. Tuberk. **55**:289, 1930.

Lachmann, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:407, 1931.

Liebermeister, G.: Ztschr. f. Tuberk. **62**:83, 1931.

Loeschcke, H.: Beitr. z. Klin. d. Tuberk. **68**:251, 1928; **81**:171, 1932.

Lubarsch, O.: Virchows Arch. f. path. Anat. **213**:417, 1913.

Lydtin, K.: Beitr. z. Klin. d. Tuberk. **67**:235, 1927; Ztschr. f. Tuberk. **49**:1, 1928; **57**:153, 1930.

Mischkowsky, R.: Ztschr. f. Tuberk. **67**:17, 1933.

Neumann, W.: Beitr. z. Klin. d. Tuberk. **40**:1, 1919.

Oberndorfer, quoted by Pagel.

Orsós, F.: Beitr. z. Klin. d. Tuberk. **70**:504, 1928.

Pagel, W.: Deutsche med. Wchnschr. **57**:2094, 1931; Ztschr. f. Tuberk. **65**:197, 1932; Ergebn. d. ges. Tuberk. **5**:231, 1933.

Lungentuberkulose, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 3, pt. 2, p. 139.

Pinner, M.: Am. J. Roentgenol. **31**:442, 1934.

Puhl, H.: Beitr. z. Klin. d. Tuberk. **52**:116, 1922.

Ranke, K. E.: Ausgewaehlte Schriften zur Tuberkulosepathologie, Berlin, Julius Springer, 1928.

Rich, A. R.: Bull. Johns Hopkins Hosp. **47**:181, 1930.

Rubinstein, H.: Beitr. z. Klin. d. Tuberk. **70**:773, 1928.

Spitzenprozesse, Leipzig, Johann Ambrosius Barth, 1934.

Schmincke, H.: Ztschr. f. ärztl. Fortbild. **26**:105, 1929.

Schmorl, G.: München. med. Wchnschr. **48**:1995, 1901; **49**:1379, 1902.

Schuermann, P.: Beitr. z. path. Anat. u. z. allg. Path. **83**:551, 1930; Schweiz. med. Wchnschr. **63**:1145, 1933.

Siegen, H.: Beitr. z. Klin. d. Tuberk. **63**:143, 1926.

Simon, G.: Beitr. z. Klin. d. Tuberk. **67**:467, 1927; **81**:194, 1932.

Stefko, W. H.: Beitr. z. Klin. d. Tuberk. **82**:566, 1933.

Straub, H.: Ztschr. f. klin. Med. **121**:515, 1932.

Sweany, H. C.: Am. Rev. Tuberc. **27**:559, 1933.

——Cook, C. E., and Kegerreis, R.: Am. Rev. Tuberc. **24**:558, 1931.

Tendeloo, N. P.: Krankheitsforschung **6**:159, 1928; Beitr. z. Klin. d. Tuberk. **6**:329, 1906.

Terplan, K.: Am. Rev. Tuberc. **29**:77, 1934.

Ulrici, H.: Beitr. z. Klin. d. Tuberk. **77**:267, 1931; **81**:183, 1932.

Wessler, quoted by Fishberg.

Wurm, H.: Beitr. z. path. Anat. u. z. allg. Path. **75**:399, 1925; **79**:209, 1927; Beitr. z. Klin. d. Tuberk. **81**:707, 1932; Klin. Wchnschr. **13**:41, 1934.

Zeiss, B.: Beitr. z. Klin. d. Tuberk. **64**:463, 1926.

News and Notes

University News, Promotions, Resignations, Appointments, Deaths, etc.—Herman A. Heise has been appointed director of the laboratories in the Columbia Hospital and the Children's Hospital in Milwaukee.

Otto Folin, professor of biologic chemistry in the Harvard University Medical School, Boston, died on October 26, at the age of 67.

George R. Minot and William P. Murphy of Harvard University Medical School, Boston, and George H. Whipple of the University of Rochester, New York, have been awarded the Nobel Prize, 1934, "for liver treatment in anemia."

Kornel L. Terplan, research professor of pathology in the University of Buffalo School of Medicine, has been been appointed head of the department of pathology and bacteriology to take the place of Herbert U. Williams, retired.

Santiago Ramón y Cajal, the great Spanish neurologist and histologist, died on October 18, at the age of 83.

Carlos Chagas, director of the Oswaldo Cruz Bacteriological Institute in Rio de Janeiro, died on November 8, at the age of 55. He described the form of trypanosomiasis of the thyroid which is found in the interior of Brazil and known generally as Chagas' disease.

Carl L. Spohr has been made acting head of the department of pathology in the Ohio State University College of Medicine, Columbus, taking the place of the late Ernest Scott.

John A. Kolmer has resigned as professor of medicine in Temple University.

A department of bacteriology has been established in the University of Southern California, Los Angeles, under the direction of Carl C. Lindegren, recently assistant in microbiology at the Mellon Institute, Pittsburgh.

Edwin O. Jordan, formerly chairman of the department of hygiene and bacteriology in the University of Chicago, was awarded the Sedgwick Memorial Medal for distinguished service in public health at the meeting of the American Public Health Association in Pasadena last September.

Society News.—The Society of American Bacteriologists will hold its thirty-sixth annual meeting in Chicago, on December 27 to 29, 1934.

The Fifteenth International Physiological Congress will be held in Leningrad and Moscow from August 9 to 17, 1935, under the presidency of Ivan P. Pavlov.

Resolution in Respect to Radiodermatitis.—The following resolution was adopted by the American Radium Society at the Cleveland Session on June 12, 1934:

"WHEREAS, It has been proven that radium and x-rays, when used properly, and in sufficient quantity, are efficient in the treatment of cancer in certain locations, and

"WHEREAS, There is a general fear in the public mind from x-ray or radium burns, which because of this fear, prevents competent radiologists from using sufficient radium or x-ray to produce the best results.

"*Be It Resolved,* That we as radiologists recognize that in the treatment of malignant disease, it is often necessary to carry the treatment on to the extent of producing a violent reaction in the surrounding tissues, which may cause the skin to peel, and blisters to form, in order to give sufficient treatment to overcome the malignant disease. We believe, therefore, that it is justifiable to produce a second degree radiodermatitis when necessary.

This resolution has been approved by the Section on Radiology of the American Medical Association and by the American College of Radiology.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE FLOW AND COMPOSITION OF LYMPH IN RELATION TO EDEMA. A. A. WEECH, E. GOETTSCH AND E. B. REEVES, J. Exper. Med. **60**:63, 1934.

The capacity of the lymphatics for removing fluid from the tissues greatly exceeds the rate at which freshly formed tissue fluid can be made available for removal. Edematous regions can be rendered nonedematous by the application of measures which activate the lymphatics, such as massage, passive motion or normal exercise. During continuous activity the rate of lymph flow is at first variable and later relatively constant. The constant rates of flow must correspond to the production of fresh lymph. A study of the constant rates indicates that the formation of lymph in edema is certainly only slightly greater, and possibly not greater, than under conditions of normality. When the protein of the plasma decreases, the protein of the lymph is also lowered. Loss of protein takes place at a faster rate from the lymph than from the plasma, so that the serum protein-lymph protein quotient is greater for the edematous than for the normal animal. In edematous animals the concentration of protein in the lymph is of the same order of magnitude as the concentration in the edema fluids. The two fluids are not, however, identical in composition. Minor fluctuations in the protein content of the lymph always occur during a period of continuous collection. The factors involved in the circulation and accumulation of tissue fluid are discussed. Reasons are given for offering the following suggestions: Significant differences in tissue pressure or tension exist between the states resulting from quiescence and activation of the lymphatics. The differences give rise to variations in the relative areas of capillary wall functioning for filtration, and reabsorption may be completely in abeyance. A decline in the proteins of the plasma may be associated with a diminished permeability of the capillaries. Such a lowering of capillary permeability would account for two features, both of which have been demonstrated: (1) failure to observe an appreciable increase in the rate of lymph formation in the edematous animal, and (2) the extremely low concentration of protein in the lymph from edematous animals. Although the difference between the protein concentrations of edema fluid and lymph from the same region is small, the conclusion is not yet justified that a similarly small difference exists between normal tissue fluid and normal lymph.

FROM THE AUTHORS' SUMMARY.

FATE OF BILIRUBIN IN THE SMALL INTESTINE. M. S. SACKLEY, C. G. JOHNSTON AND I. S. RAVDIN, J. Exper. Med. **60**:189, 1934.

Since there was no loss of bilirubin from the jejunal loop, and no loss of bilirubin when pigment was incubated with juice from the loop segment, or juice from the entire small intestine, it may be concluded that intestinal juice per se has no effect in converting bilirubin to urobilin in a two hour period, and that in the jejunal loop there was no absorption of pigment or conversion to urobilin. The experiments showing loss of pigment in the entire intestinal tract suggest that in some place other than the jejunal portion of the intestine the combined activity of the intestinal contents and intestinal cells does affect the bilirubin in the intestine. Whether the loss of bile pigment under such circumstances is due entirely to conversion, to conversion and absorption or to absorption of bilirubin as such remains to be answered by subsequent investigations.

FROM THE AUTHORS' SUMMARY AND CONCLUSIONS.

EXPERIMENTAL HETEROTOPIC FORMATION OF DENTIN AND ENAMEL. C. B. HUGGINS, H. R. MCCARROLL AND A. A. DAHLBERG, J. Exper. Med. **60**:199, 1934.

The formation of dentin and enamel in the abdominal wall of the young pup was achieved by transplantation of the soft tissues of the developing tooth germ. An interesting finding was the cytomorphosis of the epithelium of the enamel organ. When this was transplanted so that the ameloblasts were in contact with the odontoblasts the cylindric character of the epithelial cells was preserved and enamel was produced; otherwise the cylindric shape of these cells was lost and a stratified epithelium resulted, resembling the gingival epithelium and certain tumors (the adamantinoma) of the jaw and related structures. This degenerated epithelium did not produce enamel and had an important characteristic of not forming cysts in a closed connective tissue space—forming, instead, islands and cords of cells with epithelial pearl formation. Thus the influence of mesodermic connective tissue derivatives on the form and function of epithelium is presented. The odontoblasts were found capable of survival as such and readily formed new dentin in transplantation; the stellate cells of the pulp were inert from the standpoint of inducing calcification.

FROM THE AUTHORS' SUMMARY.

THE EFFECT OF THE GAMMA RAY OF RADIUM ON WOUND HEALING. IRA T. NATHANSON, Surg., Gynec. & Obst. **59**:62, 1934.

Under standard conditions of distance and filtration but with varying dosages, the gamma ray of radium was used in the treatment of surgically produced wounds in dogs. Small and moderate doses produced an acceleration of healing in wounds exposed immediately. Greater amounts gave opposite results. In wounds 24 hours old, healing was always retarded, the degree varying directly with the dose. In those 48 hours old only the higher dosages employed slowed the healing process. Retardation did not interfere with the formation of a smooth scar.

FROM THE AUTHOR'S SUMMARY (W. C. HUNTER).

INFLUENCE OF SPLENIC AUTOLYSIS ON THE LIVER. N. FIESSINGER AND A. GAJDOS, Ann. d'anat. path. **10**:141, 1933.

The authors studied the changes following extensive crushing of the spleen in dogs and guinea-pigs. Blood and urine changes in general, such as those relating to urea, cholesterol, chlorides, etc., were of no significance, except that several days after the crushing of the spleen a marked bilirubinuria developed. This was traced to extensive degenerative and atrophic changes which developed in the hepatic parenchyma at that time. These changes were followed by focal scarring of the liver. But at the time when the traumatized splenic tissue underwent organization a second type of change in the liver occurred. This consisted of an extensive proliferation of the reticulum of the liver. This proliferation appeared suddenly and simultaneously with the organization of the crushed splenic tissue. The authors agree with Guy Albot that there are two types of reaction of the hepatic mesenchyma, namely, sclerosis and reticulosis. Another interesting conclusion is that the mesenchyma throughout the body or in various organs may be stimulated by a single factor at the same time.

PERRY J. MELNICK.

NORMAL AND PATHOLOGIC OSTEOGENESIS. G. DUBREUIL, M. CHARBONNEL AND L. MASSE, Ann. d'anat. path. **10**:225 and 337, 1933.

The first paper is an extensive discussion of the classic and recent theories of osteogenesis. The essentials of the classic theory are as follows: In a vascular and connective tissue medium specialized cells appear, the osteoblasts, which elaborate osteoid tissue; the latter fixes calcium salts and thus becomes bone. Recent modifications of this theory by Heitz-Boyer and Scheikewitch and by Leriche and Policard have been widely accepted, especially by surgeons. Based on the fact that new bone can replace boiled bone pegs, bone fragments, etc., and

that transplanted periosteum does not form bone, these new theories relegate the osteoblasts to the background. Heitz-Boyer and Scheikewitch believe ossification to be a passive phenomenon which follows proper local concentration of calcium and depends on a preexisting inflammatory process. When the proper conditions irritate the periosteum (fracture, etc.) a proliferation of connective tissue results (vegetative osteitis). When this connective tissue finds a proper concentration of calcium it is transformed into bone. The cellular elements, therefore, have no specific character. Leriche and Policard have taken much the same view, and have analyzed in detail the various steps in the process. There are first an edematous loosening and modification of the connective tissue medium and other changes in the mesenchyma, which then becomes transformed into an osteoid tissue, the fibroblasts thus becoming osteoblasts without their having exerted any kind of specific influence. The preexisting local concentration of calcium is an important element in determining the steps in this process. The elaborate work of Leriche and Policard has gained wide acceptance.

Dubreuil, Charbonnel and Masse analyze each step in the theories in detail, and bring out various types of evidence to refute them. From the domains of embryology, histology, cytology and pathology they present a number of facts to prove that the osteoblasts are a specific type of cell, and that they elaborate within their cytoplasm a substance which is secreted and deposited as osteoid tissue, which then becomes calcified. They contend, therefore, that the essentials of the old classic theory of osteogenesis still hold.

In the second paper they report an extensive series of experiments which support the conclusion that the rôle of the osteoblasts is a specific one. The experimental work was done on dogs; various bones were incised, holes were bored, the periosteum was lifted or removed, with or without boring holes, pieces of bone were lifted or removed, and so on. Also, various bones were exposed to roentgen rays. Microscopic studies of the experimental material were made. In general, clearcut evidence of the specific activity of the osteoblasts could be seen. The authors therefore conclude that the classic theory of osteogenesis is still tenable. They credit Leriche and Policard and others with having stimulated much beneficial research and with having favorably influenced bone surgery, but they do not agree with their views as to the passive or inanimate nature of osteogenesis.

PERRY J. MELNICK.

EXPERIMENTAL NEPHRITIS. H. VASSILIADIS, Ann. d'anat. path. **10**:703, 1933.

By injecting uranium nitrate, corrosive mercuric bichloride, cantharides or bismuth intravenously into rabbits Vassiliadis succeeded in producing renal lesions. These were acute, subacute or chronic, depending on the dose. He claims to have demonstrated glomerular lesions in the rabbits with ascites or anasarca, but no significant glomerular changes in those without water retention. In rabbits with slight water retention only a certain number of injured glomeruli were found. In most of the rabbits with toxic nephritis this condition was either not exudative or associated with only a very little exudate.

PERRY J. MELNICK.

EXPERIMENTAL STUDY OF CEREBRAL HEMORRHAGE. H. T. DEELMAN, Ann. d'anat. path. **10**:977, 1933.

Two series of experiments were made to shed light on the question: Is cerebral hemorrhage the result of rupture of a blood vessel or due to hemorrhage by diapedesis following angiospasm? In one experiment a small amount of blood (0.5 cc.) was injected under pressure into the brains of several rabbits, thus imitating exactly the conditions of hemorrhage by rupture. The result was a massive hemorrhage which had the same characteristics as the human, namely, necrosis of the brain tissue, spreading of the blood along the perivascular spaces, necrosis of the smaller vessels and punctiform or annular hemorrhages at the periphery of the large one. In a second experiment finely ground glass suspended

in cocoa butter was injected into the carotid artery in several rabbits. The glass particles partially occluded the lumens of the smallest blood vessels, imitating the partial occlusion occurring in angiospasm. The result was typical cerebral hemorrhage resembling the former in every way. Deelman concludes that there is no single etiology. Both factors may produce the same results, in some cases rupture; in other cases, angiospasm.

PERRY J. MELNICK.

APOPLECTIC ATTACKS AND THEIR PATHOGENESIS. P. SCHWARTZ, Ann. d'anat. path. **10**:995, 1933.

Schwartz presents a clear discussion of the pathogenesis of cerebral apoplexy. In the middle of the nineteenth century Virchow's studies on embolism and thrombosis led him to conclude that these were the factors involved. Charcot and Bouchard in 1868 concluded that rupture of a cerebral aneurysm was a cause of hemorrhage. In the following half century the idea gradually became established that rupture of a blood vessel was involved. Pick and Ellis in 1910 invoked the idea of pseudo-aneurysms. But in 1918 Rosenblath established clearly that in the vast majority of cases of cerebral hemorrhage no ruptured blood vessel can be demonstrated. The classic work of Gustave Ricker of Magdeburg furnished the explanation. His experimental research showed that capillaries and arterioles are controlled by nerve impulses. Under the proper conditions, spasm of the blood vessels leads to anemia of the part supplied, then to capillary dilatation of the adjacent segment (parastasis), followed by hemorrhage by diapedesis from the dilated capillary. Attacks of cerebral vascular spasm in hypertension, then, result in encephalomalacia (anemic or nonhemorrhagic apoplexy) and, if more severe, to secondary diapedetic hemorrhage. This process explains the majority of cases of both nonhemorrhagic and hemorrhagic cerebral apoplexy in hypertension. Thrombosis, embolism and ruptured aneurysm are also found, but are rare.

PERRY J. MELNICK.

PATHOGENESIS AND PHYSIOPATHOLOGY OF CEREBRAL HEMORRHAGE. J. LHERMITTE, Ann. d'anat. path. **10**:1010, 1933.

The paper is a general discussion of the theories of the pathogenesis of cerebral hemorrhage and a short résumé of the physiologic basis for the clinical symptoms. Virchow, Charcot, Bouchard, Löwenfeld, Pick and Ellis are responsible for the theory that cerebral hemorrhage is due to the rupture of a blood vessel, either at the site of an atheromatous plaque or following necrosis of the wall of a blood vessel or rupture of an aneurysm. This theory has been strongly contested by Rosenblath, Westphal and Baer, Schwartz and others. The theory that circulatory changes, namely, vascular spasm, may be the cause, based on the work of Ricker, has gained much acceptance (Schwartz, Cohn and others). A third theory, that such hemorrhages are due to degenerative changes of the brain tissue, necrobiosis, has been proposed by Rochoux and others. A fourth theory considers that a combination of circulatory changes with preexisting degenerative changes of the brain tissue is responsible. Lhermitte favors the latter theory.

PERRY J. MELNICK.

DEVELOPMENT OF NEW BLOOD VESSELS IN GRANULATION TISSUE IN A CELLULOID CHAMBER. E. MANZ, Frankfurt. Ztschr. f. Path. **45**:464, 1933.

A method is reported by which one can study living granulation tissue with the aid of a transparent celluloid chamber implanted in the rabbit's ear. By this method it was found that new capillaries arise only from preexisting capillaries. There is no evidence that they can be formed by cells other than capillary endothelial cells. The opinion is expressed that the stimulating factor for the new formation of capillaries is not the local hyperemia but, very probably, a growth-promoting substance, apparently produced by leukocytes.

W. SAPHIR.

THE MECHANISM OF SECRETION IN THE THYROID GLAND. HARALD OKKELS, Acta path. et microbiol. Scandinav., supp. 16, 1933, p. 303.

Cytologic studies of the thyroid gland were made in guinea-pigs stimulated with extract of the anterior lobe of the pituitary gland. Thirty minutes after intraperitoneal injection of this extract the thyroid cells began to swell enormously. One hour after the injection the Golgi apparatus became visible; at the same time there were vacuolation and emptying of the colloid. The metabolism rose rapidly during the first thirty to sixty minutes; after a slight decline it remained nearly constant at a rather elevated level. The degree of metabolic activity corresponded to the degree of enlargement of the Golgi apparatus. The mitochondria in the thyroid cells seem to play an important rôle during the formation of colloid. Iodine stimulates this feature of thyroid secretion but does not influence the Golgi apparatus. The mechanism of secretion in the thyroid gland is twofold; it comprises the formation and the absorption of colloid. The unique position of the gland from a histophysiologic point of view is due to its faculty of storing a provisional secretion outside the cells in larger quantities and for a longer time than any other gland. The mitochondria are considered responsible for the formation of the secretion, whereas the Golgi apparatus is involved in its ultimate discharge.

JACOB KLEIN.

A CASE OF PANMYELOSIS. G. de OLIVEIRA, Virchows Arch. f. path. Anat. **292**: 203, 1934.

Oliveira gives the name "panmyelosis" to a condition characterized clinically and anatomically by an increase in erythrocytes, leukocytes and megakaryocytes. The clinical picture was that of erythremia or polycythemia vera; anatomically myelosis was the striking feature. A woman, aged 39 years, had had clinical symptoms for fourteen years. The erythrocyte count was 5,500,000; normoblasts were present in the peripheral blood. The leukocyte count varied at different periods from 10,000 to 110,000. The blood at the height of the illness contained 15 per cent myelocytes, 12 per cent promyelocytes and 6 per cent myeloblasts. In spite of a platelet count of 360,000 there was marked tendency to hemorrhage. The active formation in the bone marrow of erythrocytes and their precursors, myeloid cells and megakaryocytes, is interpreted as evidence of the origin of these three lines of cells from a primitive mesenchymal stem cell. Extramedullary formation of the three lines of cells in the lymph nodes and spleen was noted.

O. T. SCHULTZ.

HEMORRHAGIC THROMBOCYTHEMIA ASSOCIATED WITH ATROPHY OF THE SPLEEN. E. EPSTEIN AND A. GOEDEL, Virchows Arch. f. path. Anat. **292**:233, 1934.

A man, aged 56 years, had been under observation for four years prior to his death. His first symptoms were bleeding from the gums and interstitial hemorrhages, especially of the thighs. At this time he had an erythrocyte count that varied from 5,000,000 to 7,250,000 and a leukocytosis of from 12,500 to 14,600 with a monocytosis of from 12 to 20 per cent and an eosinophilia of from 6 to 14 per cent. The platelets varied in number between 1,800,000 and 2,200,000; in stained preparations they appeared abnormal. In these preparations there were seen also Howell-Jolly bodies and nucleated erythrocytes. The condition at this time was believed to be polycythemia vera. In the course of the disease the erythrocyte count decreased, reaching 2,730,000 before death, with 1,700 nucleated erythrocytes. The terminal leukocyte count was 12,000. The platelet count remained well over a million throughout the course of the disease. The most striking finding at necropsy was a markedly atrophied spleen; it measured 4 by 2.5 by 1.5 cm. and weighed 7 Gm. Microscopically it consisted chiefly of sclerotic, very thick-walled arteries; between these was a small amount of collagenous tissue. The bone marrow contained many megakaryocytes. Hirschfeld described hematologic obser-

vations similar to these following splenectomy. The atrophy of the spleen is ascribed to arteriosclerosis of this organ, the process being likened to that which takes place in the arteriosclerotic contracted kidney.

O. T. SCHULTZ.

EXPERIMENTAL STUDIES OF TISSUE LYMPH FLOW AND RESORPTION. H. LOESCHKE, Virchows Arch. f. path. Anat. **292**:281, 1934.

The path of tissue lymph flow was studied by means of injections of colloidal solutions directly into various tissues and organs and into serous cavities, joints and the subdural space. Trypan blue was found most satisfactory for this purpose. Animals of a variety of species were used. The solution traveled along the spaces of the loose connective tissue. It flowed also along the fibers of dense connective tissue, the solution having a strong affinity for collagenous and elastic tissue. There was active flow through the fibrous capsules of the abdominal and thoracic organs. In the connective tissues the flow was reversible, and the color disappeared after a time, in marked contrast to the prolonged retention of the dye selectively stored in granular form by the reticulo-endothelial system. Parenchymatous cells sometimes stained diffusely; these were believed to be injured cells. Resorption occurred chiefly by way of pericapillary lymphatic spaces and was most active in tissues with a rich capillary network. Adipose tissue, wherever situated, was looked on as a most active and almost specific organ of resorption. Resorption was also active in voluntary muscle. During periods of capillary distention the fluid flow was from the blood stream into the pericapillary lymphatic; during contraction of the capillary the flow was in the opposite direction. The experiments furnished evidence that material injected into the peritoneal cavity is excreted by the liver, kidney and gastro-intestinal tract. The path of excretion was directly through the organ by way of the tissue spaces. The bearing of the experiments on the deposition of amyloid and hyalin, the spread of bacteria and the metastasis of tumor cells is briefly discussed. In chronic hydrops of serous or joint cavities, active resorption by the pericapillary lymphatics of adipose tissue leads to hypertrophy of this tissue.

O. T. SCHULTZ.

Pathologic Anatomy

THE MYOCARDIAL ASCHOFF BODY. L. GROSS and J. C. EHRLICH, Am. J. Path. **10**:467 and 489, 1934.

The clinical histories and anatomic material of seventy cases of uncomplicated rheumatic fever with Aschoff bodies in the myocardium were investigated. A classification of Aschoff bodies is suggested, based on the appearance and distribution of the collagen, argentophil fibers, cell cytoplasm and nuclei. This classification includes seven types of Aschoff bodies, which apparently bear some relation to the life cycles of the lesions. Each type is described and is considered to possess sufficient characteristic features to identify it as an Aschoff body specific for rheumatic fever.

It appears that these specific lesions pass through three stages in development. The earliest phases, represented by small cell coronal and reticular Aschoff bodies, have been found to occur up to the fourth week after the onset of the illness. The middle phases, represented by large cell coronal, syncytial coronal, mosaic and large irregular cell polarized Aschoff bodies, have been found to occur between the fourth and thirteenth weeks after the onset of the illness. The late phases are represented by polarized Aschoff bodies which occur from the ninth to the sixteenth week after the onset of the illness, and subsequently by fibrillar Aschoff bodies which occur after the thirteenth week of the illness. The earliest types of specific lesions are apparently influenced in their response by the reactivity of the tissue, depending on whether there has or has not been a previous attack of rheumatic fever, and also by the state of the collagen present in the interstices between the myocardial bundles. As a consequence, the evolution of the lesion may follow one or two main courses, determined by the initial lesion. The latter may

occur in the form of the reticular or the small cell coronal Aschoff body. The final phases of the life cycle of the Aschoff body are common to both main courses. With division of the material into four groups representing different clinical courses, there appears to be some change both in the incidence of the types of Aschoff bodies in the myocardium and in their localization. The observations reported here, however, can by no means be considered as furnishing sufficient statistical evidence on which to base final conclusions on this point. That the tempo of the life cycle may be considerably faster or slower than what has been described in this report seems very probable. Some of the stages in the model of the life cycle presented by us may be absent in some cases, abbreviated in others—or, indeed, may appear in an order the reverse of that which we have suggested. These facts can be determined with greater accuracy only after a much more extensive series of cases has been examined and, in the last analysis, must await confirmation by the hitherto unsuccessful transmission of this disease to animals. It is hoped, however, that further studies will be made along these lines in order that some of these interesting relations may be placed on a firmer footing.

FROM THE AUTHORS' SUMMARIES.

THE DISAPPEARANCE OF GLOMERULI IN CHRONIC KIDNEY DISEASE. A. R. MORITZ and J. M. HAYMAN JR., Am. J. Path. **10**:505, 1934.

The number of possibly patent glomeruli and glomerular scars has been estimated by a combination of injection and histologic methods. The average number of glomeruli in fourteen normal human kidneys was 1,282,800 ± 32,700. In chronic renal disease not only the number of patent glomeruli but the total number of recognizable glomerular structures was reduced. This was most marked in chronic glomerular nephritis. The number of possibly patent glomeruli frequently falls below 500,000 and may fall below 200,000. The total number of recognizable glomerular structures, including scars, was frequently below 600,000 and in some instances below 300,000. Since large numbers of glomeruli may disappear during the course of chronic renal disease, it is suggested that the final histologic pattern may not give as much information concerning the pathogenesis or severity of the disease as is commonly thought.

FROM THE AUTHORS' SUMMARY AND CONCLUSIONS.

THE STRUCTURAL CHANGES IN THE DIGESTIVE TRACT IN UREMIA. R. H. JAFFÉ and D. R. LAING, Arch. Int. Med. **53**:851, 1934.

The diphtheritic ulcerative processes which were encountered in 19.8 per cent of 136 cases studied could be traced to localized circulatory disturbances. The earliest changes consist of capillary hyperemia of the mucosa, increased production of mucus and dilatation of the small veins of the submucosa. The increased permeability which is associated with the extreme widening of the small blood vessels leads first to edema and later to hemorrhages. Bacteria from the intestinal content settle in the devitalized hemorrhagic areas of the mucosa and cause fibrinous exudation and necrosis. The necrotic parts are sequestrated, and ulcers are formed. Attention is called to the occurrence of a pseudomembranous ulcerative colpitis in uremia, the pathogenesis of which is identical with that of the intestinal lesions.

FROM THE AUTHORS' SUMMARY.

PNEUMOCOCCAL LIPOID NEPHROSIS AND THE RELATION BETWEEN NEPHROSIS AND NEPHRITIS. S. S. BLACKMAN JR., Bull. Johns Hopkins Hosp. **55**:1, 1934.

Evidence is collected from classic examples of lipoid nephrosis described in the literature and from the study of ten cases in children that nephrosis is a form of diffuse nephritis in which microscopic hematuria, secondary anemia of hemolytic origin and slight elevation of the blood pressure may all occur at times as part of the disease. Acute cases occur without insidious onset. In these both the

neutral fats and the doubly refractile cholesterol esters in the kidneys may be very meager. The nonprotein nitrogen of the blood is not constantly or progressively elevated.

The lesions in the kidneys consist chiefly of certain diffuse changes in the epithelium of the glomeruli and tubules, identical in kind with those which may occur in any nephritis. The disease may persist for a long time, at least in children, without the development of other lesions in the majority of the glomeruli. Scarred glomeruli may be found in small numbers. There is no evidence that these focal scars are secondary to changes in the tubules.

No changes in the glomerular capillaries can be recognized to account for the albumin in the urine. The most important histologic distinction between nephrosis and nephritis depends on the absence of coagula within the glomerular capsules in nephrosis; their presence in glomerulonephritis has not been fully determined, but seems obviously related to the excretion of fibrinogen in the urine in addition to albumin.

In the cases of nephrosis described, fat deposits were present in tissues other than the kidneys. In general, the amount of fat in the liver parallels that stained in the kidneys. The significance of the fat deposits in the tissues, including the doubly refractile cholesterol esters in the kidney, is entirely unknown. The presence of neutral fat and cholesterol esters is in no sense specific for lipoid nephrosis. In the kidneys the fat in the epithelium of the tubules of the cortex is found predominantly in segments of the convoluted tubules which lie in each cortical labyrinth. Although the epithelial cells of the tubules in the cortical rays show other alterations, varying from cloudy swelling to necrosis and regeneration, these cells contain scarcely any fat deposits. The edema of nephrosis cannot be explained by mechanical factors alone. There is good evidence that widespread capillary damage is one important factor in the pathogenesis of the edema.

There is no evidence that lipoid nephrosis is a metabolic disease. Data are presented which point to an etiologic relation between chronic pneumococcic infection and the pathogenesis of lipoid nephrosis in some cases. This is supported by the experimental reproduction of nephrosis in animals by means of pneumococcus toxin, which is to be described separately. FROM THE AUTHOR'S SUMMARY.

TUMOR OF A SUBCUTANEOUS GLOMUS. MICHAEL L. MASON and ARTHUR WEIL, Surg., Gynec. & Obst. **58**:807, 1934.

The tumor is rare, benign and nonrecurring and is characterized by painful crises radiating from a small bluish subungual or subcutaneous swelling on the extremities and by a peculiar angioma-like structure richly supplied with nerve fibers. Its resemblance to neurogenic tumor on the one hand and angioma on the other, together with the fact that special stains are required for the demonstration of the true nature of the growth, probably accounts for its not being recognized as an entity. The growth reported developed under the skin of the knee following an accident thirty-seven years previously; it was exquisitely painful, about 5 mm. in diameter, bluish red and connected with the underlying tissue by means of a blood vessel. It consisted of numerous blood vessels surrounded by epithelioid and spindle cells between which were isolated myelinated and unmyelinated nerve fibers. The authors regard the tumor as a hyperplastic glomus arising from a normal structure and for this reason urge that it be classified as a hamartoma or a hyperplasia rather than a blastoma. W. C. HUNTER.

STRICTURE OF THE RECTUM FROM INGUINAL LYMPHOGRANULOMA. DAVID BLOOM, Surg., Gynec. & Obst. **58**:827, 1934.

The Frei test for inguinal lymphogranuloma was positive in three men and five women with rectal stricture. All were benefited by the usual treatment for this condition, so that it appeared fairly certain that the strictures were produced by the virus of inguinal lymphogranuloma. In four instances the lower part of

the rectum was involved while in the other four the whole rectum was affected. The fact that the genital lymphatics drain toward the rectum and the fact that this drainage differs in the two sexes explain the more frequent occurrence of rectal stricture and the lesser incidence of involvement of the inguinal nodes in women suffering from inguinal lymphogranuloma. The examination of rectal tissue from five patients revealed only simple or chronic productive inflammation. Opinion is divided as to whether stricture of the rectum associated with inguinal lymphogranuloma is due to lymphostasis with resultant fibrosis or is the direct effect of the virus. Bloom feels that most if not all of such conditions as esthiomene, anorectal syphiloma and so-called benign strictures of the rectum are identical and are due to the virus of inguinal lymphogranuloma.

W. C. HUNTER.

FENESTRAE AND POUCHES IN THE BROAD LIGAMENT AS A CAUSE OF STRANGULATED HERNIA. ARTHUR B. HUNT, Surg., Gynec. & Obst. **58**:906, 1934.

This form of internal hernia is rare and probably is the least common of the intra-abdominal strangulated hernias. Only thirteen authentic cases of strangulation through defects of the broad ligament were found recorded in the literature, and only two cases in which such defects were present but unassociated with strangulation. This condition, however, probably is more common than the reported cases would indicate. In cases in which pouches were the associated defects, congenital anomalies may be strongly suspected. Distention and distortion of the broad ligament from pregnancy or pelvic tumors seem the most likely factors in the production of fenestrae in that structure. Older multiparae are almost exclusively affected, although nulliparous women are not immune. The Baldy-Webster operation may be looked on as an etiologic factor.

FROM THE AUTHOR'S SUMMARY (W. C. HUNTER).

AN EARLY HUMAN EMBRYO IN SITU. ROBERT TENNANT AND ELIZABETH M. RAMSEY, Surg., Gynec. & Obst. **58**:968, 1934.

Macroscopically the site of the embryo appeared as a pale yellowish elevation 3 mm. in diameter and was surrounded by a halo of reddened endometrium. The primitive nature of the chorionic villi, the size of the blastocyst, the relative sizes of the amnion and yolk sac and the dimensions of the embryonic parts indicated that the embryo was of approximately the same age as the Peters embryo, namely, from 10 to 12 days.

W. C. HUNTER.

ENTEROGENOUS CYSTS. SAMUEL MCLANAHAN AND HARVEY B. STONE, Surg., Gynec. & Obst. **58**:1027, 1934.

Enterogenous or enteric cysts may occur along any portion of the gastrointestinal tract, but are most common in the ileocecal region and least common in the rectal area. They are composed of intestinal elements which may show great variations. Their origin is usually traced to the small diverticula of the intestine occurring in fetal life, and it is thought that the diverticula and cysts appearing later are different phases of the same process. Such an origin aids in explaining the location of the cysts with respect to the intestinal wall. Two cysts of this nature are reported, one in an adult of 48 years and one in an infant of 1 month. In each case the tumor lay in close association with the rectum and was successfully removed. Microscopically the cysts had the structure of rectum with some variations in the epithelial morphology.

FROM THE AUTHORS' SUMMARY (W. C. HUNTER).

NEPHROSIS OR NEPHRITIS? J. S. DUNN, J. Path. & Bact. **39**:1, 1934.

The essential lesion in subacute hypotonic edematous nephritis is in the glomeruli and consists of abnormal permanent patency of their capillaries, which

may have resulted from previous inflammation. In accordance with the modern theory of renal activity, this lesion interferes with the kidney's excretion of water and salt by causing an imbalance of filtration and reabsorption, with the latter in excess. Albuminuria is a result of the same lesion and probably depends on the mechanical factor of dilatation rather than on abnormal permeability of the glomerular capillary walls. The high percentage of albuminuria is due to concentration in the tubules. The prominent tubular changes are secondary to the lesions in the tufts and have no important functional significance.

FROM THE AUTHOR'S CONCLUSIONS.

THE LATERAL GENICULATE BODIES AS VISUAL PATHWAYS. I. MACKENZIE, J. Path. & Bact. **39**:113, 1934.

Research on cerebral localization during the past fifty years has proceeded mainly on the lines of an attempt to correlate the activities of motor and sensory organs with the functions of cortical areas, the structure and delimitation of which have been accurately defined. The present contribution is made at a time when attention is being directed to the structure and functional relationships of the intermediate seats of integration. Among these the lateral geniculate bodies have acquired a prominent place, and the evidence which has been adduced explains (1) their anatomic and physiologic disposition, (2) their relationship to the eyes and to the cerebral cortex, and (3) their participation in the construction of the special neural system which provides the anatomic substratum for visual sensation.

ON EPITHELIAL CYSTS OF THE RENAL PELVIS, URETER AND BLADDER. G. H. WILSON, J. Path. & Bact. **39**:171, 1934.

Epithelial cysts in the mucous membrane of the renal pelvis, ureter and bladder are the result of chronic inflammation. Cystic pyelitis and cystic ureteritis are mainly the result of degenerative changes occurring in epithelial inclusions, but may also be derived from the closure of folds in the mucous membrane. Cystic cystitis usually affects the trigon and is probably chiefly caused by closure of pre-existing lacunae. Spontaneous healing may occur in some cases, and all traces of cysts and epithelial inclusions may disappear. The cysts or epithelial inclusions may be followed by tumor formation. FROM THE AUTHOR'S CONCLUSIONS.

IS FATTY DEGENERATION OF THE HEART MUSCLE A PHANEROSIS? J. H. DIBLE, J. Path. & Bact. **39**:197, 1934.

In all cases of fatty change in the heart which have been investigated in this study there has been an increase in fat in the effected portion of the muscle. The evidence indicates that this change is of the nature of a simple infiltration with depot fat. There is no evidence of a process of phanerosis.

FROM THE AUTHOR'S CONCLUSIONS.

THE PULMONARY FIBROSIS OF HAEMATITE MINERS. M. J. STEWART and J. S. FAULDS, J. Path. & Bact. **39**:233, 1934.

A number of hematite miners in the West Cumberland mine field (Great Britain) have died with a grossly fibrotic lesion of the lungs in which silica and hematite dusts are present in large amount. Fifteen cases were investigated in the present study. All the patients died within the last three years. The lesion is a highly characteristic one, mainly on account of the hematite dust present, which causes the densely fibrosed areas to assume a bright brick-red color. The fibrosis is diffuse rather than nodular, often massive, and always most intense in the upper half of each lung. An associated or superimposed tuberculosis is the rule, being present in eleven of the fifteen cases. A characteristic clinical and roentgenographic picture is produced, and the diagnosis can usually be made with reasonable certainty a year or more before the fatal issue. In fourteen cases

the silica content of the lungs averaged 1.66 per cent of the dry weight. This may be compared with 1.72 per cent for a group of eight cases of ordinary silicosis and 1.78 per cent in a series of seven sandblasters examined by the same method. We are of the opinion that this lesion is a form of silicosis (siderosilicosis) resulting from the inhalation of silica-containing hematite dust generated by dry-drilling and shot-firing, and that serious trouble commenced only when the old "hammer and jumper" gave place to the dry mechanical drill. The use of the wet drill has diminished the risk to a certain extent only, as the speeding up of the drilling process has allowed blasting to take place at much shorter intervals, greatly increasing the dustiness of the atmosphere, as compared with the period prior to 1913. It is not possible at present to give even an approximate idea of the frequency of this condition. The number of persons at risk for varying periods of time during the past twenty years must run into some thousands, and it is clear from inquiry in the mine field that a certain proportion of them are suffering from this disease. The fifteen deaths from this cause recorded here occurred within the past three years, and it is unlikely that this includes all the deaths from siderosilicosis during that period. FROM THE AUTHORS' CONCLUSIONS.

ANATOMIC CHANGES IN THE DIAPHRAGM FOLLOWING PHRENICECTOMY. W. S. STANBURY, Tubercle **15**:300, 1934. See also Am. Rev. Tuberc. **29**:528, 1934.

In all but one of eleven cases the operation of choice was evulsion by the method of Felix. The duration of the paralysis varied from three weeks to six years. Atrophy of the diaphragm is evident as early as the third week after section of the phrenic nerve and is complete by the fourth month. After paralysis, one half of the diaphragm is elevated and eventrated into the thorax. With stretching it becomes a whitish membrane of parchment-like thinness. Histologically, the atrophy of the paralyzed half is complete and uniform. In one case only, a few normal muscle bundles were seen in one area, scattered among atrophic fibers. This probably represented an accessory nerve supply. There was marked distortion of the abdominal viscera in ten of the cases, in three of which a fatal gastroduodenal obstruction developed.

HISTOLOGICAL CHANGES IN THE LIVER OF 66 CHINESE INFECTED WITH CLONORCHIS SINENSIS. R. HOEPPLI, Chinese M. J. **47**:1125, 1933.

In sixty-six Chinese who for the greater part had met a more or less sudden death which was in no case apparently due to clonorchis infection, Clonorchis sinensis was accidentally found in the liver at autopsy. With the exception of one case the infection was always light or moderate. In the majority of the cases the larger bile ducts showed dilatation, thickening of the wall and formation of numerous glandular structures. Only two cases of hepatic cirrhosis were found, one of Laennec's type and one of portal cirrhosis corresponding in type to the cirrhosis parasitaria described by previous authors and probably due to clonorchis infection. Increase of periportal tissue in a varying degree was observed forty-nine times; infiltration with eosinophils, in thirty-seven cases; fatty changes of liver cells, frequently connected with atrophy of liver cells in the center of the lobules, was found twenty times. In five cases, the central veins were surrounded by newformed fibrous tissue, and in four cases there occurred a thickening and hyalinization of the intima of small arteries. The results of the examination of the present material indicate that probably in many cases of moderate clonorchis infection in which the clinical symptoms are light or nonexistent already considerable histologic changes may be present in the liver. FROM THE AUTHOR'S SUMMARY.

DIAPHRAGMATIC HERNIA. C. CONTAT, Ann. d'anat. path. **10**:1, 1933.

A case of congenital true diaphragmatic hernia in a boy 18 months old is presented. The hernia was parasternal and bilateral. Only three similar cases have been

reported. A discussion of diaphragmatic hernia follows. Congenital false hernia forms over 86 per cent of the cases, is five times more frequent on the left side, and affects boys more frequently than girls. It results from a failure of fusion of the diaphragm during the third month of fetal life. Congenital true hernia is characterized by a sac composed of thinned-out diaphragm. Several theories regarding its formation include: diminished resistance of the diaphragm, asymmetrical development of the liver, and anomalous and insufficient blood supply to the diaphragm, with atrophy of the muscle fibers. PERRY J. MELNICK.

IDIOPATHIC HYPERTROPHY OF THE HEART. J. C. POMPE, Ann. d'anat. path. **10**:23, 1933.

A case of idiopathic hypertrophy of the heart in a girl 7 months old is described. The heart weighed 190 Gm. (normal 36 Gm.). Histologic examination revealed marked infiltration of the cardiac muscle fibers by glycogen. In addition, almost every other organ in the body was also infiltrated by glycogen. The literature on idiopathic hypertrophy of the heart is reviewed, and to the various theories of etiology another is added, namely, that the condition springs from a disturbance of glycogen metabolism. Seven cases recorded in the literature were similar histologically, but glycogen was demonstrated in only a few.

PERRY J. MELNICK.

SUBCUTANEOUS PERIARTERITIS NODOSA. K. LINDBERG, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:159, 1933.

Two cases of periarteritis nodosa are reported in detail, and twenty-one cases recorded in the literature are reviewed. In some instances the vascular nodules are subcutaneous. In these the diagnosis may be aided by biopsy. The condition may occur in association with influenza, angina, erysipelas, suppurating wounds, diphtheria, articular rheumatism, gonorrhea and syphilis. It is considered by many to be a nonspecific hyperergic reaction to infection. The prognosis is serious because of possible involvement of the viscera. However, in one third of the reported cases the disease ran a benign course. JACOB KLEIN.

ATYPICAL LYMPHOGRANULOMATOSIS. H. PFENNINGWERTH, Frankfurt. Ztschr. f. Path. **44**:85, 1932.

Pfenningwerth believes that lymphogranulomatosis (Hodgkin's disease) may be atypical in regard to location, course and microscopic picture. It may involve the skin, spinal column, ribs, bone marrow, brain, dura, eye, parotid gland, nasopharyngeal space, thyroid, thymus, thoracic duct, trachea, lungs, pericardium, pancreas, liver, spleen (a completely isolated form), suprarenal glands, ovaries, uterus, placenta, testes, epididymis and prostate. It may take the course of cryptogenic sepsis, acute degeneration of the myocardium, infectious cholangeitis, generalized tuberculous lymphadenopathy or lymphatic leukemia. Atypical lymphogranulomatosis may be characterized morphologically by a marked preponderance of lymphocytes, plasma cells, eosinophilic cells, epithelioid cells or giant cells. But it also may show only a small number of cells of any one of these types. The giant cells may resemble megakaryocytes or cells with phagocytic properties. As a result of irradiation with roentgen rays the epithelioid and giant cells may shrink and connective tissue fibers increase. Granulomas that consist of cells of the types seen in Gaucher's disease or that resemble diffuse reticulo-endotheliosis should not be considered typical lymphogranulomatosis. The diagnosis of atypical lymphogranulomatosis should never be made on the ground that any other somewhat similar disease can be ruled out. In other words, a diagnosis of atypical lymphogranulomatosis *per exclusionem* should not be made. O. SAPHIR.

Pathologic Chemistry and Physics

ACID-BASE BALANCE OF GASTRIC JUICE, BLOOD AND URINE BEFORE AND AT INTERVALS AFTER STIMULATION OF THE GASTRIC JUICE BY HISTAMINE. L. MARTIN, Bull. Johns Hopkins Hosp. **55**:57, 1934.

A number of persons were studied to observe the electrolyte changes in the gastric juice, blood and urine during the period of gastric secretion. Histamine was used as a stimulant, and the gastric juice was continuously extracted during the period of observation. The subjects are described under two groups: (1) those who were able to secrete free hydrochloric acid into the gastric juice and (2) those who were not. The amount of salts lost from the body in group 1 was about four times that lost in group 2. In the blood of the first group the typical changes were a decrease of chloride and phosphate and an increase of carbon dioxide content and serum protein. There was a slight rise of total serum base. This represents a state of relative alkalosis. The urine became more alkaline in the majority of cases. Among the anions, chloride and phosphate fell while carbon dioxide increased. Of the cations, base, hydrogen ion concentration and ammonia nitrogen fell. In the group with achlorhydria the variations in the majority of the cases were similar in kind but different in degree from those in group 1. The difference in degree consisted of a smaller loss of electrolyte in the gastric juice and correspondingly smaller variations in the blood and serum. In the initial specimen certain distinctive differences between the groups were noted. In group 2 the carbon dioxide capacity of the serum more frequently fell and the blood chloride more often rose, although the rises were small. In the urine the change of p_H was apt to be less marked, and in a larger percentage of cases the urine became more acid or remained unchanged.

FROM THE AUTHOR'S SUMMARY.

A PHYSICO-CHEMICAL STUDY OF THE SACHS-GEORGI REACTION. E. M. DUNLOP AND S. SUGDEN, J. Path. & Bact. **39**:149, 1934.

With nonsyphilitic serum, precipitation occurs in a limited zone of low concentrations of serum and electrolyte. It does not occur beyond this zone. With syphilitic serum, precipitation occurs in the same zone as with nonsyphilitic serum and also in a zone of high concentrations of serum and electrolyte. These two zones are essentially discontinuous. The precipitate obtained with syphilitic serum in the zone of low concentrations is similar in composition (nitrogen content) to the precipitate obtained with nonsyphilitic serum in the same zone, but different in chemical composition from the precipitate obtained with syphilitic serum in the zone of high serum and high electrolyte concentrations. The difference in behavior of syphilitic and nonsyphilitic serum in the Sachs-Georgi test is dependent on a qualitative difference between the two types of serum.

FROM THE AUTHORS' SUMMARY.

THE CONVERSION OF THE GLYCOGEN OF THE VAGINA INTO LACTIC ACID. R. CRUIKSHANK, J. Path. & Bact. **39**:213, 1934.

A series of observations and experiments was made to find out how the glycogen in the vaginal epithelium of infants and adult women is converted into lactic acid. The results indicated that the production of this acid is due principally to bacterial fermentation of the glycogen. Further, in vitro experiments have shown that Döderlein's vaginal bacillus, a member of the lactobacillus family, and it alone of the organisms likely to be present in the vagina as saprophytes or pathogens, is capable of directly fermenting glycogen with the production of lactic acid. Other lactobacilli, such as B. bifidus, B. acidophilus-odontolyticus, ferment glycogen late, after from seven to ten days' incubation, a delay which may be due to lack of habituation to this carbohydrate. On the other hand, B. bulgaricus,

which is used therapeutically in the treatment of vaginal discharges, failed to ferment glycogen. These findings do not explain the moderate degree of acidity in the bacteria-free vagina of the new-born infant or the lactic acid in hematocolpos fluid. An attempt to demonstrate a nonbacterial enzyme in vaginal secretion failed, but in view of the glycogenase in fresh serum, the glycogen in the vaginal cells may in the absence of bacteria be converted by such an enzyme to dextrose, from which in turn lactic acid is produced by a glycolytic cellular enzyme.

FROM THE AUTHOR'S SUMMARY.

EXPERIMENTAL ASPERGILLOSIS OF THE SPLEEN. A. NANTA AND M. SENDRAIL, Ann. d'anat. path. **10**:677, 1933.

An experimental study was undertaken to determine if the scleropigmentary Gamna-Gandy nodules in the spleen in so-called mycotic splenomegaly are really of mycotic origin. The authors injected several varieties of Aspergillus intravenously and also locally into the spleen in dogs and rabbits. They were able to demonstrate that a number of species of Aspergillus heretofore considered innocuous are pathogenic. They were able to reproduce in the animals all the clinical features of splenic anemia, including the hemorrhagic, ascitic and icteric forms. Anatomically the lesions of this condition were also reproduced, including the splenomegaly, siderofibrotic nodules in the spleen, etc. Histologically the nodules were characteristic, with an outer hemorrhagic zone, a middle fibrotic zone containing giant cells and iron-filled macrophages, and an inner zone composed of long basophilic and hyaline mycelial threads. The lesions are probably formed by enzymes and local acidity produced by the fungus.

PERRY J. MELNICK.

QUANTITATIVE SPECTROSCOPIC ESTIMATION OF MANGANESE IN TISSUES. W. GERLACH AND K. RUTHARDT, Virchows Arch. f. path. Anat. **292**:52, 1934.

To Gerlach's series of contributions describing the quantitative spectroscopic elementary analysis of tissues the authors add a method for manganese.

O. T. SCHULTZ.

PEROXIDASE REACTION IN AN OVARIAN CYSTOMA. W. LOELE, Virchows Arch. f. path. Anat. **292**:135, 1934.

The columnar epithelium of some of the cystic and glandular spaces of a multilocular cystoma of the ovary was stained violet by a solution of alpha-naphthol and hydrogen dioxide. The reaction, which is dependent on the presence of naphthol peroxidase, is explained by degeneration of the cells in the presence of persistent leukocytosis.

O. T. SCHULTZ.

DISTRIBUTION OF MINERAL SALTS IN INCINERATED SECTIONS OF NECROSES AND ABSCESSES. W. KLOSTERMEYER, Virchows Arch. f. path. Anat. **292**:268, 1934.

The distribution of mineral salts in ashed sections or spodograms of tissues containing necroses and abscesses prepared by the Schultz-Brauns method was studied by the indicator method of Hackmann. The ash of necroses consisted chiefly of insoluble calcium salts, together with probably sodium phosphate. When all nuclear material had disappeared from necroses alkaline carbonates could no longer be detected. The ash of abscesses contained relatively much potassium carbonate, less sodium carbonate and no insoluble calcium salts. Leukocytic infiltration of necroses led to a decrease in calcium salts and an increase in potassium carbonate. The potassium is probably derived from the nuclei of the tissue.

O. T. SCHULTZ.

THE ALBUMIN-GLOBULIN QUOTIENT IN ALBUMINURIA. J. BING, Acta path. et microbiol. Scandinav. **11**:323, 1934.

In examinations of the albumin-globulin quotient A/G in blood and urine the calculations ought to be made with the help of the relative albumin fraction (r. A. %), i. e., the fraction of the total protein which is represented by the albumin, instead of A/G, as this method affords much more exact values. The relative albumin fraction in the urine is dependent on two factors: (1) the ratio between the protein fractions in the blood and (2) the renal factor (R) which is calculated from the relation between the relative albumin fractions in the urine and blood. Examinations before and after transfusion of blood to patients with albuminuria, in whom changes in the relative albumin fraction of the blood of up to 20 per cent were detected, showed that the renal factor was constant. If the relative albumin fraction is particularly low in patients with amyloidosis, this is due to corresponding relations in the blood and not, as was hitherto supposed, to the circumstance that the glomerules, on account of their amyloid degeneration, are particularly permeable for the globulins. In the work of Hiller, McIntosh and van Slyke the renal factor was found to be high in the case of nephrosis and low in the case of chronic glomerulonephritis. The renal factor is never found to be lower than 1. The observations recorded in this paper are supportive of the modern conception of the mechanism of albuminuria as being an excretion of plasma proteins by filtration through injured glomerules.

FROM THE AUTHOR'S SUMMARY.

Microbiology and Parasitology

THE PATHOGENESIS OF CHRONIC ULCERATIVE PULMONARY TUBERCULOSIS. E. R. LONG, Puerto Rico J. Pub. Health & Trop. Med. **9**:365, 1934.

Chronic ulcerative pulmonary tuberculosis, the adult type of pulmonary tuberculosis, or phthisis, represents reinfection, of progressive course, in a person who already has a primary focus of tuberculosis. The latter focus is commonly in the lungs, with secondary involvement of the tracheobronchial lymph nodes, but may be elsewhere; it represents a childhood type of tuberculosis that has become inactive or healed. The onset of chronic ulcerative pulmonary tuberculosis may be insidious, without symptoms, or acute, with symptoms resembling those of the commonly recognized acute respiratory infections. Anatomically it occurs in the apexes of the lungs or in the subapical region and spreads downward. The downward extension takes place by intrabronchial spread from regions of ulceration in the upper parts. The essential condition for the whole course of progression is softening of the caseous tubercle. The mechanism of this softening is not exactly understood, but the process seems related to tissue hypersensitiveness. Vast numbers of tubercle bacilli are present in softening caseous tissue, many more than in the walls of old cavities, and therefore each intrabronchial discharge of a softened mass leads to further spread within the lung, as well as to the outside world. This fact makes the softening of the caseous tubercle the key problem in the pathogenesis of tuberculosis.

FROM THE AUTHOR'S SUMMARY.

THE SINGLE PYOGENIC LIVER ABSCESS. ROBERT E. ROTHENBERG and WILLIAM LINDER, Surg., Gynec. & Obst. **59**:31, 1934.

Cultures of eleven of the twenty-four abscesses investigated were sterile. Five yielded staphylococci. Streptococci, B. mucosus-capsulatus and unidentified gram-positive bacilli each occurred twice, while the colon bacillus and the pyocyaneus bacillus were each isolated once. The pathogenesis strongly resembled that of renal carbuncle and osteomyelitis in that nine persons had antecedent focal infection, suggesting hematogenous dissemination, probably by way of the hepatic artery. In eighteen of the cases the abscess lay in the dome of the liver. Surgical drainage was followed by recovery in 58.3 per cent of the cases.

W. C. HUNTER.

THE TREATMENT OF SEPTICAEMIA IN RABBITS WITH LYMPH-GLAND FIXATION ABSCESSES. A. C. ALPORT, Brit. J. Exper. Path. **15**:175, 1934.

Fixation abscesses, obtained by the subcutaneous injection of desiccated lymph gland, were used for the treatment of septicemia in rabbits; the object was to cause leukocytosis, thus increasing the bactericidal power of the blood. Nine normal rabbits were used. Four were controls and received intravenous injections of virulent streptococci only; all died. The other five rabbits received similar doses of streptococci intravenously, but were also given subcutaneous injections of lymph gland; all these animals recovered. FROM THE AUTHOR'S SUMMARY.

THE INFLUENCE OF TEMPERATURE ON THE SURVIVAL OF PURE SUSPENSIONS OF THE ELEMENTARY BODIES OF VACCINIA. C. R. AMIES, Brit. J. Exper. Path. **15**:180, 1934.

Pure suspensions of the elementary bodies of vaccinia in a simple broth medium retain their activity for considerable periods at room temperature, and for several weeks at 37 C. FROM THE AUTHOR'S CONCLUSIONS.

EFFECT OF SPLENECTOMY IN INFECTION WITH TRYPANOSOMA CONGOLENSE IN MICE. C. H. BROWNING, D. F. CAPELL and R. GULBRANSEN, J. Path. & Bact. **39**:65, 1934.

The discrepancies in the effects of splenectomy in various protozoal and spirochetal infections in different species of animals and, in the case of S. recurrentis, apparently in infections with different strains of the parasite in the same host, suggest either that there is no common basis of defense against infections which seem to be similar in their pathology or else that the function of the spleen as an organ of defense must vary considerably according to the species.

A LUMINOUS ORGANISM IN RELATION TO NUTRITION ON AGAR. J. CRUIKSHANK, J. Path. & Bact. **39**:141, 1934.

A study was made of the factors concerned in the growth of colonies of a luminous organism on agar plates. By using the light produced by the colonies, recorded photographically, as a measure of their metabolic activities, it was shown that diffusible food substances are rapidly consumed from the agar in the neighborhood of the colonies and subsequently from agar at a distance. The volume of uninoculated agar from which the organisms may ultimately draw nourishment is the important factor in determining the amount of their growth. The same factor appears to be of importance in the colony growth of other organisms.

FROM THE AUTHOR'S SUMMARY.

THE BLOOD IN RATS AND MICE AFTER SPLENECTOMY, WITH OBSERVATIONS ON BARTONELLA MURIS AND EPERYTHROZOON COCCOIDES. J. A. W. MCCLUSKIE and J. S. F. NIVEN, J. Path. & Bact. **39**:185, 1934.

In mice removal of the spleen is occasionally followed by anemia and the appearance of bartonellae in the red corpuscles. The bodies are much smaller than those observed in the rat. A more frequent occurrence is the appearance of peculiar ring-shaped structures in the blood—Schilling's Eperythrozoon coccoides—some of which are free and some attached to the red cells. Attempts to infect both normal and splenectomized rats with eperythrozoon-containing blood have been without success. Attempts to isolate Bartonella muris and Eperythrozoon coccoides by various cultural methods have been unsuccessful. The evidence afforded by the morphology and staining reactions of the bartonella bodies of rats, by their incidence and behavior after splenectomy and by their transmissibility, as well as by the lesions accompanying their appearance, points to their being distinct from any of the tissue constituents of the host and suggests strongly that they

are micro-organisms. In the case of Eperythrozoon coccoides of the mouse the evidence is less strong but points in the same direction. The question is left open as to where these organisms are situated in the host during the latent periods.

CULTIVATION OF THE GONOCOCCUS. J. W. MCLEOD and others, J. Path. & Bact. **39**:221, 1934.

Cultural demonstration of the gonococcus is superior to demonstration by examination of smears in chronic cases of gonorrhea in both sexes and in all cases in females, specially when material for examination is taken from the cervix. There is, however, a residue of cases in which the smear is positive and the culture negative which, with the methods at present available, is larger than can be explained by falsely positive results. A small percentage of falsely positive results is undoubtedly recorded if diagnosis is determined by microscopic examination of Gram-stained smear preparations only. The cultivation of many strains of the gonococcus is prompted by incubation in air containing carbon dioxide in the concentration of 8 per cent. The recognition of gonococcal colonies in a culture is greatly facilitated by the use of the direct oxydase reaction, and the employment of this reaction results in a marked economy of time.

FROM THE AUTHORS' CONCLUSIONS.

THE ACTION OF EXTRACTS OF STAPHYLOCOCCI GROWN ON CELLOPHANE AGAR. LUISE BIRCH-HIRSCHFELD, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:260, 1933-1934.

The culture medium of Jacobsthal is made by coating a thick layer of agar with cellophane. The crystalloid substances of the medium pass through the cellophane; the colloidal products of bacterial metabolism remain on the surface. Some bacteria grow abundantly on such medium, but they become quickly autolyzed. Birch-Hirschfeld used this technic for the study of staphylococcic hemolysin and protease. Hemolysin could be separated from the protease by precipitation with certain concentrations of acetic acid; both were precipitated with ammonium sulphate. Their thermoresistance was marked. Heating above 60 C. destroyed them gradually, but even after one-half hour at 100 C. from one twentieth to one tenth of the original titer was retained. Addition of dextrose to the culture medium interfered markedly with the formation of hemolysin, but had only a slight effect on that of protease; on the other hand, addition of blood enhanced the titer of the hemolysin; the production of protease was adversely affected, but only when the addition of blood amounted to 20 per cent or more. A normally nonhemolytic strain of streptococci became hemolytic when grown on cellophane agar, and another strain acquired marked toxicity under similar circumstances.

I. DAVIDSOHN.

SEASONAL FLUCTUATIONS OF SPONTANEOUS INFECTIONS IN GUINEA-PIGS. T. KJÄR, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:511, 1933-1934.

Of 3,860 guinea-pigs which were treated with diphtheria toxoid during two years, 6.5 per cent died from intercurrent infections. The largest number of deaths occurred in March and April, which coincided with the minimum antibody response to diphtheria antigen. The smallest number of deaths was observed in August and October, which coincided with the optimum antibody response.

I. DAVIDSOHN.

Immunology

THE VALUE OF THE NEGATIVE INTRACUTANEOUS TUBERCULIN TEST (MANTOUX) IN ADULTS. M. R. LICHTENSTEIN, Am. Rev. Tuberc. **29**:190, 1934.

Complete insensitivity to tuberculoprotein makes it certain that the patient is nontuberculous, with few exceptions (moribund or highly toxic patients, for a

variable period after harboring a contagious disease or after a course of tuberculin therapy). Patients who react only to strong concentrations of tuberculoprotein, with the same exceptions, almost certainly have no active tuberculosis.

H. J. Corper.

The Rôle of Multiple Reactive Groups in Antigen-Antibody Union as Illustrated by an Instance of Cross-Precipitation. M. Heidelberger and F. E. Kendall, J. Exper. Med. **59**:519, 1934.

Antiserums to R-salt-azo-benzidine-azo-crystalline egg albumin give precipitates with crystalline egg albumin by virtue of their antidye content. The quantitative course of the reactions with increasing amounts of antigen is very similar for the dye-antidye and egg albumin-antiegg albumin systems, but differs markedly for the cross-reaction between egg albumin and antidye serum. A possible explanation for the occurrence of this one-sided cross-reaction is given in terms of reactive groupings on the antigen and antibody. A qualitative expression of the course of the cross-reaction is given in terms of the laws of classic chemistry.

From the Authors' Summary.

Failure to Neutralize Poliomyelitic Virus by the Serum of Macacus Rhesus. N. P. Hudson, E. H. Lennette and E. Q. King, J. Exper. Med. **59**:543, 1934.

Twelve specimens of serum from nine adult male monkeys failed to neutralize the virus of poliomyelitis. Ten samples of serum obtained from three adult female monkeys at various phases of the menstrual cycle likewise proved incapable of neutralizing the virus. An eleventh serum, drawn from a fourth female thirty-two days post partum, gave irregular results. It neutralized once and failed to do so on second test. This is the only suggestion in our experiments that a physiologic factor may play a part in immunity to poliomyelitis. Fourteen serums from ten immature monkeys caused to menstruate by treatment with anterior pituitary extract were devoid of virucidal property. This treatment failed also to induce a systemic resistance to intracerebral injections of virus in the nine monkeys of the same group available for testing. We were unable to demonstrate in our monkeys a correlation between the virucidal capacity of the serum and maturity or physiologic variations as exemplified by menstruation.

From the Authors' Summary and Conclusions.

Serum Diagnosis in Leprosy. J. Laigret, Arch. Inst. Pasteur de Tunis **22**:509, 1933.

A ground, heated and concentrated extract from the bacilli of rat leprosy was injected intradermally into four lepers and into controls. Three of the four lepers reacted, whereas three of the four controls failed to react. Complement-fixation tests were all positive, but syphilitic serum and tuberculous serum, especially the former, reacted in the few tests made. For this antigen, acetone and methyl alcohol were used to extract the rat leprosy bacilli. The possible value of negative serologic tests and the suggestion of antigenic similarity in human and rat leprosy were pointed out.

M. S. Marshall.

A Test for the Confirmation of the Serologic Diagnosis of Syphilis. Ernst Witebsky, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:323, 1933.

By means of Landsteiner's technic Witebsky separated the syphilitic antibody from the precipitate produced in the syphilitic serum with the citochol or Kahn antigens. The fluid with the antibodies, which was practically free from proteins, reacted positively in complement-fixation and flocculation tests. Sometimes a

positive reaction was observed when the native serum reacted negatively. That is explained by the elimination of inhibitory substances during the process of separation of the antibodies from the precipitate. The result adds the final link to the chain of proofs first furnished by Sachs, Klopstock and Weil that the changes in the syphilitic serum are an antigen-antibody reaction and not merely a result of colloidal imbalance. The procedure makes it possible to differentiate positive from certain falsely positive reactions. However, it will not help to differentiate syphilis from conditions in which lipoid antibodies are developed (trypanosomiasis, acute malaria).

I. DAVIDSOHN.

THE GROUP-SPECIFIC B-RECEPTORS AND THEIR ANTIBODIES. KURT MARBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:340, 1933.

Marberg reinvestigated the B quality in the red blood cells of the rabbit and man. He confirmed the previous report of Friedenreich and With by means of different procedures. The B quality in human red cells has some factors in common with the B quality in the rabbit cells, but they are not identical, as evidenced by the fact that the human anti-B (β) iso-agglutinin was in most instances absorbed by rabbit red cells quite as well as by human cells of type B, while the anti-B hetero-agglutinin of rabbit immune serums, produced by inoculation of the rabbits with human B cells, was absorbed only by human B cells but not by rabbit cells. The latter phenomenon is in full agreement with established serologic facts. Occasionally human anti-B iso-agglutinin was not fully bound by rabbit red cells. Human saliva of group B had a powerful binding effect on the agglutinating properties of the rabbit anti-B immune serum. The binding was not affected by boiling.

I. DAVIDSOHN.

ACTIVE SUBSTANCES AND FUNCTIONAL CHANGES IN ANAPHYLACTIC SHOCK. W. ZECHNALL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:357, 1933.

Zechnall found an increase of potassium in the blood of shocked, actively sensitized guinea-pigs (from 25.7 to 43 mg. as compared with 21 mg. per hundred cubic centimeters in normal animals). A like increase was found during shock in passively sensitized guinea-pigs. The elimination of intravenously injected potassium in actively sensitized guinea-pigs was delayed. Contrary to the report of Jelin, intravenous injection of glycogen did not produce anaphylactic shock in the normal and in the sensitized guinea-pigs.

I. DAVIDSOHN.

INFLUENCE OF SNAKE VENOM ON THE HAPTENS. WALTER SCHEPERS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:395, 1933.

When alcoholic extracts of different types were mixed with weak dilutions of cobra venom, they failed to show the usual flocculation with antiserums. Cobra venom alone did not inhibit flocculation if it was added to the mixture of antiserum and alcoholic extract without preliminary incubation with the extract. Schepers explains the action as being due to the formation of nonspecific inhibitory substances by combination of the venom with certain lipoids of the haptens.

I. DAVIDSOHN.

EXPERIMENTAL ANAPHYLAXIS IN GUINEA-PIGS WITH PLANT ANTIGEN. P. MANTEUFEL and O. WICHELHAUSEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:460, 1933.

Watery extracts of beans (Phaseolus vulgaris) and of peas (Pisum sativum) were injected intravenously into twelve rabbits. All the animals produced good precipitating serums. The older reports in the literature concerning normal precipitins against legumes were not confirmed. The method of passive anaphylaxis was a less reliable means than the precipitin test for the study of the antigenic

relations between the different varieties of the legumes. The Arthus phenomenon was less sensitive and less specific for the study of the sensitivity of guinea-pigs than was the active anaphylactic shock. The conjunctiva and the nasal mucosa of sensitized guinea-pigs did not react to local applications of the antigens. The Prausnitz-Küstner phenomenon was elicited in guinea-pigs sensitized with legumes but not in those sensitized with pollens. The seroreactions, the estimation of precipitins, the complement-fixation reaction, the passive anaphylaxis and the test of Prausnitz-Küstner are not to be depended on as reliable tests for the determination of sensitivity in guinea-pigs. Manteufel and Wichelhausen maintain that by the same token there is no justification for the strict separation of human allergy from experimental anaphylaxis in animals because the former fails to show some or all of the aforementioned serologic reactions. Attempts at desensitization of sensitized guinea-pigs were not successful. Administration of different anticoagulants and artificial production of fever did not prevent the development or decrease the intensity of the anaphylactic shock in actively sensitized guinea-pigs.

I. DAVIDSOHN.

Tumors

DIBENZANTHRACENE 1:2:5:6 AS A CARCINOGENIC AGENT. M. G. SEELIG, Am. J. Cancer **20**:827, 1934.

Seelig states that his work, on the whole, has confirmed the facts developed by the English workers. He found dibenzanthracene to be a cleaner, simpler, more manageable compound than tar. It is less toxic, and this makes possible the development of tumors in a larger percentage of mice than one can hope to secure with tar. On the other hand, the time necessary for the development of the tumors is markedly longer than with tar. When time is an important factor it might be much more desirable to use tar. Another disadvantage is the cost. The cost of high fraction tar is practically negligible, whereas Seelig paid $3.50 a gram for dibenzanthracene.

FROM THE AUTHOR'S CONCLUSIONS.

SOMATIC MUTATION IN THE ORIGIN OF CANCER. M. R. CURTIS, W. F. DUNNING AND F. D. BULLOCK, Am. J. Cancer **21**:86, 1934.

The number of independent cysticercus tumors per host was related directly to the number of parasitic cysts. In the hosts with 1, 2 and 3 probably independent tumors the most frequent numbers of cysts per host were, respectively, from 1 to 6, from 6 to 11 and from 16 to 21. That is, an increase in the number of cysts per host was accompanied by an increase in the number of multiple primary cysticercus tumors. Both the cysticercus cysts and the cysticercus tumors were distributed to the several lobes of the liver in proportions approximately equal to the relative weights of the lobes. This indicates a chance distribution of both the cysts and the tumors. Rats which were infested with the larvae of Taenia and also inoculated subcutaneously with cysticercus sarcoma from another host sometimes acquired both a transplanted and a primary cysticercus tumor, sometimes neither and sometimes either one without the other. Indirect evidence indicates that the interval from the time the tumor could be recognized until it proved fatal was on the average about twenty-four days. The larvae from malignant cysts were not significantly longer than those from benign cysts of the same age, indicating that the sizes of the enclosed larvae were not a factor in determining which cysts became malignant. Of 4,321 cysticercus tumors, 79.3 per cent were sarcomas of the large cell type and probably arose from the cells which formed the inner zone of the cyst wall; 20.6 per cent were sarcomas composed of smaller cells and possibly arose from the outer zone of the cyst wall; 6 were adenomas, and 1 was a carcinosarcoma, which must have arisen from the snared-off bile-duct and hepatic epithelium which was embedded in the wall of the cyst. That is, the types of cysticercus tumors observed represent the types of cells found in the

cyst wall, and each type is represented by a number consistent with the expectation that the change of a normal cell to a tumor cell results from the chance action of an irritant.

FROM THE AUTHORS' SUMMARY.

CANCER CELLS IN THE BLOOD STREAM. E. H. POOL and G. R. DUNLOP, Am. J. Cancer **21**:99, 1934.

A hitherto undescribed large cell was found in smears of blood from seventeen of forty persons with cancer. Apparently the same cell was found in the blood of one noncancerous patient. The significance and origin of the cell are not established.

CONTAGIOUS LYMPHOSARCOMA OF DOGS. W. A. DEMONBREUN and E. W. GOODPASTURE, Am. J. Cancer **21**:295, 1934.

The tumor-inducing agent is destroyed by drying, freezing, glycerination and mechanical means. No evidence was obtained that a virus or any other infectious agent separable from the cells is concerned in the etiology of the disease. It is concluded that contagious lymphosarcoma is a true neoplasm and is transferable by the inoculation of living tumor cells in ulcerated surfaces. The origin of the tumor cells is not definitely determined, but they are probably derived from the lymphocytic series. The presence of neutral fat droplets in the tumor cell is recorded as characteristic. Multiple tumors can be induced by intravenous injections of the tumor cells in suspension. Growth of the tumor is associated with a variable immunity to reinoculation, and metastases seem to be related to periods of low resistance or absence of resistance which may occur during stages of massive and active tumor growth. A substantial immunity may be broken down by injection of large quantities of tumor cells. Serum obtained from rabbits immunized with emulsions of the tumor tissue is capable of destroying the tumor cells in vitro, and prevents the appearance of a tumor following inoculation of the treated cells. Serum obtained from rabbits immunized with normal dog serum affects tumor cells in vitro only slightly, and fails to prevent their growth when injected subcutaneously into dogs. The action on tumor cells of the heterophilic antibodies contained in such antiserums is negligible. Further studies are required to demonstrate definitely the presence of specific antibodies in the serum of animals immunized with emulsions of this tumor.

FROM THE AUTHORS' SUMMARY.

PITUITARY HORMONE IN CANCER. F. BISCHOFF, L. C. MAXWELL and H. J. ULLMANN, Am. J. Cancer **21**:329, 1934.

Sublethal doses of radiation to the pituitary gland, which brought about a temporary cessation of body growth, significantly retarded the growth rate of rat sarcoma R10, rat carcinoma 256 and a mouse carcinoma (spontaneous mammary) if the tumor appeared at the period of maximum retardation of the body weight. In the case of rat carcinoma 256, these effects were abolished by a simultaneous dosage of pituitary extracts with standardized growth-promoting powers. A cessation of increase in body weight produced by various poisons, equivalent to that following irradiation of the pituitary gland, failed to retard tumor growth significantly. In older rats dosage with standardized growth-promoting preparations of the pituitary gland significantly accelerated the rate of growth of carcinoma 256. In younger animals with mouse sarcoma 170 and rat sarcoma 10 the effect was less significant. Dosage of the urine of pregnancy augmented the effect of irradiation of the pituitary gland on the rate of growth of mouse sarcoma 180. The effect on rat carcinoma 256 and rat sarcoma 10 was less significant. Attempts to abolish permanently the function of the anterior lobe of the rat or mouse through irradiation of the pituitary gland were unsuccessful.

FROM THE AUTHORS' SUMMARY.

EFFECT OF THE ANTERIOR PITUITARY HORMONES ON THE GROWTH OF MOUSE SARCOMA. O. F. KREHBIEL, C. D. HAAGENSEN and H. PLANTENGA, Am. J. Cancer **21**:346, 1934.

Out of sixty treated animals fifteen survived the period of observation. Of these fifteen, seven had tumors which were slightly smaller than the tumors in the controls, while the remaining eight had tumors which were as large as, or larger than, those in the controls. Since the condition of all the treated animals suffered as a result of the injections, it would be expected that their tumors would be rather smaller than those of the untreated controls. These experiments fail to show, however, any specific and marked inhibitive action of anterior pituitary hormone on tumor growth as claimed by Zondek and his collaborators. It should be noted that it has been impossible to demonstrate an inhibitive action of anterior pituitary hormone on tumor growth despite the use of doses of the hormone which are so enormous in terms of the amount of the hormone normally excreted in the adult human being that all calculations become relatively meaningless. Katzman and Doisy have calculated that the average daily prolan excretion of adult males is 8 mouse units and that of adult females 10 mouse units. Yet 200 mouse units a day did not inhibit tumor growth in mice. These facts should discourage any attempts to use anterior pituitary hormone in the treatment of human cancer.

FROM THE AUTHORS' DISCUSSION.

DOES CHICKEN BLOOD PRODUCE IMMUNITY TO RAT TUMORS? C. D. HAAGENSEN, Am. J. Cancer **21**:376, 1934.

The intraperitoneal injection of heparinized chicken blood in young rats does not produce immunity to inoculation with Walker rat carcinoma 256.

FROM THE AUTHOR'S CONCLUSIONS.

VENEREAL SARCOMA OF THE DOG. E. L. STUBBS and J. FURTH, Am. J. Path. **10**:275, 1934.

Two venereal sarcomas were successfully transmitted to healthy dogs, and one of them was transplanted in eleven successive generations. Inoculations were successful in 72 per cent of the dogs given subcutaneous injections of an emulsion of tumor cells. Tumor appeared at the site of inoculation within an average of thirty-eight days and with one exception began to regress after reaching a size of about 10 cm. in the longest diameter. In one dog the tumor spread by metastasis throughout the body. Intravenous inoculation produced generalized sarcomatosis in two of seven inoculated animals. Transmission was also successful on rubbing tumor material into the scarified surface of the glans penis. Attempts to transmit the disease through intact mucous membrane (the conjunctiva) were unsuccessful. The ability of the tumor material to transmit the disease was destroyed by the addition of 50 per cent glycerin, by desiccation, by freezing and thawing and by heating to 50 C. for one and one-half hours. Tumor material passed through siliceous filters likewise failed to produce tumors. These experiments indicate that venereal sarcoma, often designated "infectious sarcoma of dogs," is a neoplastic process and like other mammalian tumors can be transmitted only by viable tumor cells.

FROM THE AUTHORS' SUMMARY AND CONCLUSIONS.

THROMBOPENIC PURPURA IN CARCINOMA OF THE STOMACH WITH METASTASES. J. S. LAWRENCE and E. B. MAHONEY, Am. J. Path. **10**:383, 1934.

It would seem as though the presence of large numbers of tumor cells in the marrow was the probable cause of the thrombopenia, although normal megakaryocytes were present. Increased destruction of platelets in the puerperal circulation cannot be excluded.

"Heavy Water" and Tumor Growth. W. H. Woglom and L. A. Weber, J. A. M. A. **102**:1289, 1934.

Deuterium, in the amounts that it was possible to administer as "heavy water," had no demonstrable effect on the growth of mouse sarcoma 180 or mouse carcinoma 63.

From the Authors' Conclusion.

Changes in the Esterase and Fat Content of the Serum Induced by Cancer and Cancer-Producing Agents. H. N. Green, Brit. J. Exper. Path. **15**:1, 1934.

During the growth of Jensen sarcoma of the rat the esterase content of the serum falls progressively, ultimately reaching a very low level. The esterase content of the liver, lungs and kidneys is also much diminished. The phosphatase content of the serum also falls, but the average fall is less than half that of the esterase. In rats resistant to inoculation of the Jensen sarcoma the esterase content of the serum tends to rise. The fatty acid content of the serum rises in many and possibly in all rats during the growth of the Jensen sarcoma. It may reach a maximum level approaching 2 per cent, and then falls during the terminal stages of the tumor's growth. There is an associated rise in the cholesterol, but to a much less degree. With tar epitheliomas of mice and localized carcinomas of man the serum esterase content ranges around the normal, with a tendency to rise slightly. Evidence was obtained that the application of tar or the inoculation of tar or of 1:2:5:6-dibenzanthracene produces a rise in the esterase content of the serum of rabbits in a proportion of the cases.

From the Author's Summary.

Medicolegal Pathology

Blood Grouping in Forensic Medicine. L. Lattes, Ann. d. méd. lég. **14**: 245, 1934.

A review of the literature reveals that the heredity of the agglutinogens M and N has been studied in 1,039 families with 2,900 children. Furthermore, in tests on 3,751 mothers with 5,912 children there was not a single exception to the theory of Landsteiner and Levine. Hence, the medicolegal application of the agglutinogens M and N for the exclusion of paternity is justifiable at present.

On the other hand, because of the difficulties in the technic and irregularities in the heredity, the subgroups of group A and group AB are of value only as confirmatory evidence for disproving paternity.

A. S. Wiener.

Precipitin Reaction of Teeth. H. Plathner, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:61, 1934.

Extracts from finely comminuted human and animal teeth give species-specific precipitin reactions. Intact human molars and wisdom teeth are exceptions; also enamel. Teeth long buried in the ground or exposed to the air may not give any reactions.

Demonstration of Group-Specific Substances in Body Fluids. G. Strassmann, Deutsche Ztschr. f. d. ges. gerichlt. Med. **23**:186, 1934.

Strassmann's studies corroborate the findings of other investigators with regard to the presence of group-specific substances in body fluids. He found iso-agglutinins present post mortem in transudates in the pericardial, pleural and peritoneal cavities, rarely in saliva and never in cerebrospinal fluid. Receptors, however, are present not only in transudates, but in saliva, semen, gastric secretions, urine, meconium, vaginal mucus, nasal secretion, sweat and stains of all these secretions. The receptors may be demonstrated by the ability of the stain to inhibit

specifically the iso-agglutinins in a group O serum. A control test with unstained material must be made to rule out the possibility of nonspecific inhibition. The receptor peculiar to group O blood may be directly demonstrated by inhibition tests with ox serum previously absorbed with human blood of group AB. The fact that in the dry state the receptors resist physical and chemical agents for periods of months or years increases the value of the tests. One must always bear in mind that not every person secretes the receptors. A. S. WIENER.

DEMONSTRATION OF CARBON MONOXIDE POISONING 144 DAYS AFTER DEATH. P. HEILMANN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:215, 1934.

It is well known that carbon monoxide has been found several weeks and months after death in disinterred bodies. A case is described in which carbon monoxide was found 144 days after death. The body was that of a man, aged 55 years, who was found dead in the morning in a room which contained two coke ovens. In spite of considerable decomposition the cherry red color was marked in the subcutaneous fat, the muscles, the blood and the organs. Carbon monoxide was demonstrated chemically and physically. No other cause of death was found.

STRUCTURAL CHANGES IN ACUTE AMMONIA POISONING. G. I. VON FAZEKAS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:225, 1934.

Ammonia acts not only as a local corrosive but as a general poison which is rapidly absorbed. In addition to laking the red cells of the blood it injures the endothelial lining of the blood vessels severely, and fatty changes develop in the internal organs, especially the liver and the kidneys. Marked lipemia may result. In the central nervous system severe alteration develops, especially in the ganglion cells of the cerebral cortex, but also of the white matter.

MAJOR PROBLEMS IN BLOOD GROUPING DURING THE PERIOD 1927-1933. L. HIRSZFELD, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **15**: 54, 1934.

This review supplements Hirszfeld's previous review on the same subject published in the same journal in 1928. The topics presented are: the heredity of the four blood groups, the subgroups of group A and group AB and their heredity, panagglutination, development of the blood groups, group-specific substances in the organs and body fluids, the agglutinogens M and N and their heredity, medicolegal applications, and individual differences in animal blood. The principal value of this review lies in its comprehensive nature and extensive 50 page bibliography. The review suffers, however, from the lack of emphasis on technic, and because the selection of material is uncritical. A. S. WIENER.

UNEXPECTED AND SUDDEN DEATH IN CHILDHOOD. S. A. SIWE, Upsala läkareförh. **39**:203, 1934.

This article is based on the study of 212 cases of unexpected or sudden death in the first fifteen years of life. Most of the cases occurred in the first months, and in the majority death was due to diseases of the respiratory organs. Such diseases may not give rise to local symptoms and are easily overlooked. Even at the necropsy the extent of the infectious lesion may be limited. In nurslings a simple coryza or a slight intestinal disturbance may lead to vomiting and aspiration, which rapidly and sometimes unnoticed end in death. In none of the cases studied did enlargement of the thymus appear to play any rôle in causing death. The possibility of respiratory aspiration does not seem to be recognized sufficiently. At the necropsy it is not enough to inspect the finer bronchi for gastric contents. Litmus paper must be used in order to be sure that aspiration of stomach contents is not overlooked.

Technical

BACTERIAL CAPSULES AS DEMONSTRATED BY A SIMPLE METHOD. J. W. HOWIE and J. KIRKPATRICK, J. Path. & Bact. **39**:165, 1934.

A simple and reliable method for the demonstration of bacterial capsules consists in adding to a loopful of exudate or of culture suspended in broth on a microscope slide first a drop of dilute carbolfuchsin, followed by a drop of 5-10 per cent solution of eosin, and then making films. The bacterial bodies are positively stained, and the capsules are seen by "relief staining." Suspending capsulated organisms in water hinders or completely prevents the demonstration of the capsules but does not destroy them. Capsules and bacterial bodies can still be demonstrated in cultures of pneumococci treated by addition of bile salt.

FROM THE AUTHORS' SUMMARY.

METHODS OF STUDY OF PULMONARY SILICOSIS. E. BEHR, Ann. d'anat. path. **10**:849, 1933.

The chief histologic methods of demonstrating the minute quartz crysals in pulmonary silicosis are discussed. Watkins, Pitchford and Moir in 1916 recommended acid digestion of the tissues. Policard and Okkels used incineration, which has the advantage of retaining the relationship of the crystals to the tissues. Giese in 1931 recommended mounting mediums for the sections which have different indexes of refraction from quartz. Behr used Giese's methods in the study of a case and found them excellent. He was surprised at the large numbers of crystals which could be seen. Three photomicrographs illustrate the relationship of the crystals to the tissues.

PERRY J. MELNICK.

A QUALITATIVE TEST FOR BARBITURATES IN THE URINE. W. MOHRSCHULZ, München. med. Wchnschr. **81**:672, 1934.

Poisoning with barbiturates, accidental or intentional, has increased during the past few years so as to be the commonest of all medicamental poisonings. These compounds appear promptly in the urine, where their detection is important in establishing barbiturate poisoning. Mohrschulz describes a simple rapid qualitative test for demonstrating barbiturates in the urine: From 15 to 20 cc. of urine is vigorously boiled with 0.2 Gm. of charcoal, centrifugated hot, the aqueous layer poured off, and the centrifuge tube dried with filter paper. The charcoal is washed into a reagent glass with 3 or 4 cc. of absolute alcohol, extracted with 7 cc. of chloroform and the mixture warmed, shaken and filtered. About 2 cc. of the filtrate (usually turbid) is clarified with small additions of absolute alcohol. To this mixture are added 20 drops of a 1 per cent cobaltic nitrate solution in absolute alcohol and then, drop by drop, a 1 per cent solution of potassium hydroxide in absolute alcohol. A dark blue coloration indicates the presence of a barbiturate.

EDWIN F. HIRSCH.

THE USE OF THE CENTRIFUGE IN THE M. K. R. II (MEINICKE CLEARING REACTION) FOR THE DIAGNOSIS OF TUBERCULOSIS, SYPHILIS AND GONORRHEA. F. E. HAAG AND AGNES DANE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:101, 1934.

The latest modification of the Meinicke precipitation test for syphilis is based on the use of a new extract and on the employment of the centrifuge. The extract contains the ether-insoluble, but alcohol-soluble fraction of beef heart to which balsam of Tolu and Victoria blue are added. A 3.5 per cent solution of sodium chloride is used as a diluent. The mixture of serum and of diluted antigenic extract is shaken and then centrifugated at 2,000 revolutions for ten minutes. The supernatant fluid is discarded, the tubes turned upside down, and the result is estimated from the appearance of the blue sediment. The same extract was applied by

Meinicke for the diagnosis of malleus, infectious abortion and gonorrhea. For that purpose the specific bacterial antigen is added to the sodium chloride solution before it is mixed with the extract. In a study of 5,239 serums, the results of the new Meinicke test were compared with those of several complement-fixation and precipitation tests for syphilis. It was found more satisfactory than the older procedures of Meinicke, and the results compared very closely with those of Müller's ball test. Its rapidity and the ease with which the results can be read are in its favor. The reaction was tested on a series of patients with gonorrhea, and it was found slightly more sensitive than the complement-fixation test but only in cases without complications; otherwise the complement-fixation test was preferable. It could not be used for purposes of differentiation in patients who also had syphilis, because then it was always positive. The new procedure was also employed for the diagnosis of tuberculosis. The antigen of Witebsky, Klingenstein and Kuhn (a benzene extract of tubercle bacilli) proved most satisfactory of a number which were tried. The results were better than any so far reported, particularly with regard to cases of tuberculosis of bones and joints, in which the previous methods were usually very disappointing. No negative results were obtained in fifty-nine clinically established cases of pulmonary tuberculosis, and on the other hand there were no positive results in thirteen cases in which the disease was known to have been clinically cured. In negative control cases, only 3.6 per cent of the results were falsely positive. The disadvantage of the method is that all patients with syphilis react positively.

I. DAVIDSOHN.

THE KAHN TEST MODIFIED BY CENTRIFUGATION. CARL SCHLESMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:467, 1934.

According to Schlesmann, there is no real need for three tubes as they are used in the standard Kahn test. He uses the middle tube only (with 0.025 cc. of the antigen), adds 0.15 cc. of serum, shakes the mixture vigorously, and places it for twelve minutes in the incubator at 37 C. (or for four minutes in the water bath at the same temperature). Then the test tube is again shaken and centrifugated for ten minutes at 2,200 revolutions. After the addition of 0.5 cc. of physiologic solution of sodium chloride, the test tube is again shaken, and the result is read. Schlesmann carried out 2,400 tests (along with the official Wassermann test, the complement-fixation test which employs the very sensitive pallida antigen, the Sachs-Georgi test and the third Meinicke precipitation test) and found that the reading was made easier and that the test was more economical than, and at least as sensitive as, the standard Kahn procedure.

I. DAVIDSOHN.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, March 27, 1934

WILLIAM C. VON GLAHN, *President, in the Chair*

A CASE OF DIABETES INSIPIDUS WITH AUTOPSY. LAWRENCE SOPHIAN.

A white woman, 33 years old, began to suffer with nausea and vomiting in August 1933. This continued, and she lost strength and weight. Clinical examination showed nothing unfavorable except a low grade fever and leukocytosis for about a week, with subsequent improvement. Polyuria and polydipsia were present, and the specific gravity of the urine was persistently between 1.002 and 1.010. There was some albuminuria, but the urine contained very few formed elements. The great weakness suggested a diagnosis of Simmonds' disease. The fluid output was from 3,800 to 7,600 cc. The intake and output were reduced by the injection of a solution of pituitary, but the patient apparently felt worse under these conditions. Roentgen examination of the bones and thorax revealed nothing. The blood chemistry, blood pressure and eyegrounds were normal. The clinical course showed an increase in apathy and a terminal subnormal temperature. The patient died after two months in the hospital.

Postmortem examination of the body showed all organs normal except the bones, the pituitary gland, the heart and the kidneys. The thyroid and suprarenal glands were examined and appeared normal with the exception of a very small fetal adenoma in the thyroid. Small streaks of opacity found in the heart and kidneys proved, on section, to be zones of necrosis with numerous gram-positive cocci in them microscopically. This appeared to be an agonal phenomenon.

The pituitary gland measured 17 by 12 by 9 mm. Near the stalk posteriorly was observed a projecting clear nodule 2 mm. in diameter. Serial sections were made through the gland and through the neighboring base of the brain, including the third ventricle. The main cyst and several smaller cysts were found to be in the pars intermedia, and were lined by simple low cuboidal epithelium. The smaller cysts contained colloid. In the neighboring portions of the posterior lobe no necrosis or proliferation of glia could be observed. The posterior lobe showed invading columns of basophilic cells. The constitution of the anterior lobe appeared normal in all portions. No ischemic or necrotic lesions were found in a search of 140 sections.

The bones on section presented a peculiar combination of osteolysis and osteogenesis. The gross change which brought this to notice was a granular roughening of the outer surface of the skull, which had a reddened appearance. On section the diploe was absent, and the bone tissue appeared softer than normal, as were the ribs and vertebrae. The type of bone change does not appear to be specific of any disease. The bone trabeculae were broadened, and the marrow channels were filled with fibrous tissue containing numerous hyperemic vessels. A considerable accumulation of osteoblasts could be found in some of these spaces. There was also new bone formation in small peripheral islands fairly well demarcated from the older bone.

The several features of this case do not appear to form any of the hitherto described syndromes. Clinically the weakness and cachexia were pronounced, but did not have the appearance of progeria as characteristically seen in Simmonds' disease. The response to the medication with pituitary solution was moderately

satisfactory in causing concentration of the urine, but the symptoms seemed to be aggravated. Histologically the basophilic infiltration of the posterior lobe appears to be the same process described recently by Cushing as an indication of activation of the posterior lobe. This would appear to be contradictory to the deficiency hypothesis ordinarily held in diabetes insipidus. As far as the bone changes are concerned, they do not appear to be similar to those in Paget's disease or to those in any of the clinical or experimental cases of hyperparathyroidism.

DISCUSSION

IRVING GRAEF: I should like to ask if the parathyroid glands were examined.

LAWRENCE SOPHIAN: I made a search for them and could not find them. I took several small pieces of tissue which I hoped were parathyroid glands, but I could not identify them afterward.

ANEURYSMS OF THE SINUSES OF VALSALVA: REPORT OF A CASE. H. D. KESTEN.

A colored youth, aged 19, who stated that he had had a chancre one and one-half years previously, followed by a rash, was admitted to the Presbyterian Hospital with intermittent complete heart block associated with an enlargement of the heart and pulmonic and apical systolic murmurs. The Wassermann test was negative repeatedly. An acute febrile polyarthritis developed following a hemolytic streptococcic angina. Death occurred two years after the appearance of the chancre, with signs of cardiac failure.

The postmortem examination was unfortunately limited to the heart. This organ was enlarged symmetrically and contained two aneurysms. One, the larger, opened by a buttonhole mouth into the base of the right aortic sinus and extended downward and posteriorly for several cubic centimeters into the interventricular septum. The other, occluded by a recently formed thrombus, lay beneath the left sinus, communicating with it. The coronary arteries were not compromised. The aortic valve cusps and arch of the aorta were normal. In the myocardium about these aneurysms were extensive areas of caseation, necrosis, numerous obliterated arterioles and collections of lymphoid and plasma cells. No spirochetes were found. The myocardium also contained characteristic Aschoff bodies. In addition, a penile scar was present. The aneurysms apparently developed as outpouchings into tissues which were necrotic and softened, probably as the result of the inflammatory obliterating endarteritis—syphilitic or rheumatic—of numerous septal arterioles.

FATAL ESTIVO-AUTUMNAL MALARIA IN DRUG ADDICTS IN NEW YORK CITY. MILTON HELPERN.

Twenty-one fatal cases of estivo-autumnal malaria of the cerebral form and one case of quartan malaria were examined post mortem by members of the staff of the Chief Medical Examiner. The fatalities occurred in a total group of forty-nine cases of malaria of which thirty-nine were of the estivo-autumnal type, nine were quartan and one was tertian, during a period from Sept. 25, 1933, to Feb. 28, 1934. In every instance the patient was a drug addict of the type employing the intravenous route for the injection of the drug. The disease was transmitted directly from addict to addict by the common use of unsterilized syringes.

Twenty of the persons who died of estivo-autumnal malaria died in coma and one of lobar pneumonia which developed several days after the temperature had dropped to normal and the parasites had disappeared from the blood. One who had quartan malaria displayed maniacal symptoms and died of bronchopneumonia.

The pathologic changes were fairly constant. In all the cases of fatal estivo-autumnal malaria in which coma developed the plasmodia were localized in great numbers in the capillaries of the brain. Parasites were not found in the brain of the patient who died of lobar pneumonia or in the brain of the one who had fatal quartan malaria. No excessive accumulation of malarial parasites was found in the capillaries of other organs.

The cerebral findings, the soft, swollen and only moderately enlarged spleens and the lack of pigmentation in the bone marrow indicated an acute course of the disease. The localization of the parasites in the brain in all the fatal cases suggested the possibility of a single strain of Plasmodium falciparum-quotidianum with an affinity for the cerebral capillaries. This was consistent with the epidemiologic findings, which indicated that the disease, after having been introduced by a carrier, was directly transmitted from addict to addict.

A complete report of the clinical, pathologic and epidemiologic observations in this series of cases is in preparation.

DILATATION OF THE PULMONARY ARTERY. B. S. OPPENHEIMER.

Idiopathic Dilatation of the Pulmonary Artery.—A study was made of seven cases which presented very similar clinical and roentgen features, which indicated a huge dilatation of the whole pulmonary arterial tree. Two of the patients came to necropsy, but no cause for the enormous dilatation of the pulmonary artery and its branches could be found. The finding of a similar dilatation in a 5 month old infant by Zuber suggests that such a dilatation may be primary and congenital, and the atherosclerosis, when it occurs, secondary. The diagnosis may be suspected clinically from the cyanosis, dyspnea, cough, secondary polycythemia, right-sided enlargement of the heart and murmur of pulmonary insufficiency; however, the characteristic feature is the striking roentgenographic evidence of a prominent pulmonary conus with large tumor-like pulsating hilar shadows which are formed by the pulmonary vessels. In the cases studied, gross examination of the heart at necropsy revealed a huge dilatation of the pulmonary artery and its main branches, a small aorta, an enormously hypertrophied right ventricle and auricle, a small left ventricle and an absence of any other congenital or acquired defect. Examination of the lungs showed that the dilatation of the pulmonary arterial tree extended peripherally almost to the pleural surface. The histologic picture of the pulmonary artery was essentially that of arteriosclerosis with intimal thickening and lipoid deposits which have not compromised the lumen. Careful histologic studies of the small arteries by Dr. Klemperer revealed only slight intimal thickening—nothing to suggest the condition described by MacCallum under the title of obliterative pulmonary arteriosclerosis. Such an idiopathic dilatation of the pulmonary artery is tentatively considered here as either the result of an unequal division of the truncus arteriosus or possibly as a gigantism, an arteriomegaly, similar to the congenital arteriectasis which occurs in the limbs and has been described by Parkes-Weber as "hemangiectatic hypertrophy of the limbs."

Dilatation of the Pulmonary Artery Associated with Cardiac Anomalies.—A clinical and roentgenographic picture similar to the foregoing occurred in a woman of gracile habitus in whom necropsy revealed, in addition to the huge dilatation of the pulmonary artery and an occluding thrombus in each of its main branches, a large congenital interauricular septal defect. A necrotizing arteritis of the pulmonary artery affecting primarily the media was found by Dr. Klemperer. The dynamics of the circulation leading to the greatly hypertrophied right ventricle and auricle are somewhat more readily understood under such conditions than in the purely idiopathic dilatation.

Still clearer from the pathologicophysiologic standpoint was another case in which the dilatation of the pulmonary artery was associated not only with an interauricular septal defect but also with an acquired mitral stenosis (Aschoff bodies were not found). Twenty-four such instances, including the one of Dressler and Roesler, have recently been collected from the literature by McGinn and White.

DISCUSSION

HUGO ROESLER (by invitation): This is a real contribution to the rather neglected field of pulmonary artery disease. The case of gigantism of the pulmonary artery may represent a new entity, provided that one is not dealing with

diffuse arteriovenous aneurysmal anastomoses of the arterial and venous system respectively. I am informed by Dr. Oppenheimer that careful histologic examination showed no evidence of arteriosclerotic changes. The dilatation of the pulmonary artery in the presence of an interatrial septal defect is characteristic indeed. The ratio of the size of the pulmonary artery to that of the aorta is on the average 3:2. The enormous enlargement of the heart, almost entirely on the right, with marked preponderance of dilatation over hypertrophy, can be understood only by assuming a left to right shunt, and these cases prove that the necessity of managing an increased amount of blood is the main stimulus for the dilatation. From a roentgenologic point of view it may be said that the enormous dilatation of the branches of the pulmonary artery has been misinterpreted and diagnosed as a tumor. The shadows of these vessels can be seen to pulsate, and when these pulsations become markedly expansile, regurgitation of the pulmonic valves must be present. The narrowness of the aortic shadow helps in the diagnostic approach. Another interesting feature of the interatrial septal defect is the preponderance of its occurrence in females.

I am glad that Dr. Oppenheimer has not used the term "Ayerza's disease." Confusion has been brought about by trying to construct clinical or pathologic entities and adding Ayerza's name to them. Ayerza himself (1901) described a clinical picture of what would now be called the decompensated stage of a cor pulmonale—a picture which had already been described in the French literature. The postmortem report of Ayerza's case does not mention the pulmonary artery, and Ayerza himself never made any statement as to the pathologic entity of this clinical syndrome. As to the primary arteriosclerosis of the lesser circulation, probably the best early macroscopic and microscopic description with the correct correlation of the clinical and pathologic pictures was given by J. Klobs *(Wchnbl. d. Ztschr. d. k. k. Gesellsch. d. Aertze,* Wien **21**:357, 1865). As Dr. Oppenheimer has pointed out, there are many causes for dilatation of the pulmonary artery, and I am demonstrating by lantern slides some roentgenograms illustrating the influence of thyrotoxicosis and pneumonoconiosis. As another interesting contribution, I present a case of congenital heart disease with enormous dilatation of the pulmonary artery and a visible lime salt deposit in it.

As Costa has pointed out, aneurysm of the pulmonary artery as compared with aneurysm of the aorta has a rather different age distribution, as well as etiology. The former is distributed about equally throughout all age groups and occurs, in almost half of the cases, in the presence of other cardiovascular malformations, and in the rest of the cases the mycotic and infectious factors surpass the syphilitic one.

THE PATHOLOGY OF MEASLES WITH SPECIAL REFERENCE TO PNEUMONIA. LAWRENCE W. SMITH.

My paper concerns itself with a review of the pathologic changes found in approximately seventy-five cases of fatal measles. The cutaneous changes and the lesions of the mucous membranes are first reviewed, showing the Koplik spot to be a periductal cellular reaction and the lesions of the skin to consist of mild hyperemia with perivascular infiltration by large mononuclear cells. The chief cause of death in measles being pneumonia, a review of the pulmonary findings is presented. These may be summarized briefly as follows: There are an acute mucopurulent bronchitis and bronchiolitis associated with marked peribronchial thickening. The peribronchial thickening is caused by fibroblastic proliferation, capillary congestion with endothelial proliferation, edema and marked mononuclear cell infiltration. It is similar to the peribronchial thickening seen in pertussis and in influenza, but the type of cell involved is the large mononuclear phagocyte. From the peribronchial thickening interstitial pneumonitis develops, which seems to be nearly specific in these three diseases—measles, pertussis and influenza. This suggests the possibility of a common etiology, as emphasized by McCordock. The other visceral changes are found primarily associated with the reticulo-endothelial system and are evidenced by infiltrations of the spleen, lymph nodes and lymphoid tissue of the

gastro-intestinal tract by large mononuclear cells, with occasional instances of interstitial nephritis. Toxic changes are seen involving the central nervous system, with the development of an encephalomyelopathy, as shown by Scheffer and Ferraro and by Krieder. In addition to the nerve cell degeneration, endothelial damage is seen, with venous thrombosis and similar endothelial cellular proliferation. In the treatment of the disease, no specific therapy has been discovered. Convalescent or parental serum has been used successfully as a prophylactic measure, and more recently similar results have been suggested in the use of placental extract prepared according to the method of McKhann.

DISCUSSION

LAWRENCE SOPHIAN: About three years ago I had occasion to examine an appendix removed from a child with measles, and at the time I was much puzzled by the appearance of certain very large cells, some multinucleated, in the lymph follicles of the appendical mucosa. About two months later Warthin's paper on the lesions of the tonsils in measles came out, and he described peculiar endothelial leukocytes or large monocytes of the same type as I saw in the appendix. I should like to ask Dr. Smith if such cells are known to occur in the lungs in the pneumonia produced in measles.

LAWRENCE W. SMITH: Yes, Dr. Sophian, they do.

In Conjunction with the Stated Meeting of the New York Academy of Medicine, April 5, 1934

WILLIAM C. VON GLAHN, *President, in the Chair*

SYMPOSIUM ON THE RECENT PROGRESS OF RESEARCH IN LEUKEMIA

EXPERIMENTAL STUDIES IN LEUKEMIA. MAURICE N. RICHTER.

A general résumé is presented of the work on lymphatic leukemia of mice carried out as a cooperative project by the Department of Genetics of the Carnegie Institution of Washington and the Department of Pathology of the College of Physicians and Surgeons of Columbia University. The report concerns mainly experiments on mice of strain C58, in which about 90 per cent of the animals living more than six months show spontaneous development of lymphatic leukemia. Four types of experimental observations are described:

1. Studies on the transmissibility of leukemia. Leukemic cells from mice of strain C58 can be carried indefinitely in normal mice of the same strain by transfer from animal to animal, the inoculated animal acquiring leukemia. In order to transmit the disease by inoculation, it is necessary to introduce living leukemic cells into the bodies of susceptible mice.

2. Cytologic studies of the leukemic cells. The cells are morphologically identical with the immature lymphoid cells of the mouse, and do not present any structural abnormalities. The chromosome number is 40, which is normal for the mouse. In inoculated animals the infiltrations do not arise by proliferation of cells of the inoculated host, but by continued growth and division of the cells introduced.

3. Metabolic studies of leukemic cells. Not only are there striking differences in metabolism between the lymph nodes of normal and leukemic animals, but also between those of mice in which different lines of cells are carried by inoculation. Thus the oxygen consumption of nodes of one line (A) is greater than that of normal nodes and of leukemic nodes of another line (I). However, aerobic glycolysis of the latter line (I) is almost three times as great as that of normal nodes or of nodes of line A. Anaerobic glycolysis in line I is about 1.5 times as great as that of normal nodes.

4. Genetic studies on the occurrence and transmissibility of leukemia. Long inbreeding of strain C58 and of other strains bred in the same laboratory has led to marked genetic uniformity in each strain. The occurrence of spontaneous leukemia in a large proportion of mice of one strain and its virtual absence in another indicate that the disease is under specific genetic control. However, some nongenetic factor is also involved, as indicated by the occurrence of a larger proportion of spontaneous cases in hybrids when the mother is from the leukemic (C58) strain.

Heredity also plays a part in susceptibility to inoculation, for leukemias arising in one strain of mice may or may not be transmissible by inoculation in mice of another strain. Thus, a mouse may be susceptible to one line of leukemic cells, but not to another. These results indicate the importance of genetic control of mice used in the study of experimental leukemia.

EXPERIMENTAL PHASES OF LEUKEMIA. J. FURTH.

Two phases of experimental leukemia are discussed: (*a*) the relation of x-rays to the lymphomatosis of mice; (*b*) avian leukosis. The former is fully described in the *American Journal of Cancer* (**19**:521, 1933) and the *American Journal of Roentgenology and Radium Therapy* (in press), and the latter in the *Journal of Experimental Medicine* (**58**:253, 1933; **59**:501, 1934) and the *Proceedings of the Society of Experimental Biology and Medicine* (**31**:921 and 923, 1934).

PATHOLOGIC ASPECT. R. H. JAFFÉ, Chicago (by invitation).

Experimental studies on leukemia in lower animals seem to lend strong support to the conception that leukemia is closely related to the malignant tumors. In human pathology, too, considerable similarities exist between leukemia and neoplasms. There is the purposeless mass production of cells of inferior biologic quality. The mitoses are atypical, resembling those seen in carcinomas and sarcomas. Isaac and Groat refer to haploid mitoses in leukemic myeloblasts. The reduction in the number of chromosomes suggests an accident in cell division resulting in the formation of viable daughter cells with abnormal growth properties and defective ability to mature. Since Banti and Ribbert, much significance has been attributed to the invasion of blood vessels by the leukemic formations.

The fact, however, that in rare cases of leukemia the leukemic process may, in one location, assume the appearance of a sarcoma with invasive, destructive growth and formation of metastases (leukosarcoma, myeloblast sarcoma) indicates that common leukemia should not be identified with malignant neoplasms. According to Naegeli and others, the long persistence of the parenchyma in organs with leukemic infiltrations (e. g., the kidneys) and the maintenance of undisturbed function by these organs are difficult to reconcile with the behavior of a malignant tumor. Under the influence of intercurrent infections (tuberculosis, erysipelas) the leukemic process may almost completely subside and the normal function of the blood-forming organs may be temporarily restored, a phenomenon not observed in the presence of malignant neoplasms. In view of these discrepancies, Helly and, to certain extent, also, Heiberg relate leukemia to adenoma rather than to a malignant neoplasm. But the invariably fatal outcome of leukemia speaks strongly against Helly's interpretation.

A close scrutiny of the histogenesis of the leukemic changes reveals, I believe, the principal differences between the neoplasm and leukemia. The sarcomas and the carcinomas start from a more or less circumscribed group of cells, and it is by unrestricted multiplication of these cells that the tumor grows and metastasizes. The majority of investigators agree on the autochthonous formation of the leukemic infiltrations, wherever they may arise, although hemorrhages may occasionally lead to the colonization of leukemic blood cells with secondary local growth (e. g., in the brain—Fried).

The question will arise as to the source of the leukemic infiltrations. Since leukemic infiltrations may occur in any organ of the body, the parenteral tissue of

these infiltrations must be widely distributed. Maximow, and with him a considerable number of recent investigators, assumes that in the mesenchyma there persists throughout life an undifferentiated germinal tissue endowed with blood cell-forming potencies. This germinal tissue, which does not store electronegative colloids or phagocytose corpuscular matter, is located between the adventitial cells of the small blood vessels. In the blood-forming organs it is inserted into the cytoplasmic reticulum. Under normal conditions the higher differentiated cells of the mesenchyma, especially the reticulo-endothelial cells (histiocytes) and the fibrocytes, do not produce blood cells. When irritated the reticulo-endothelial cells may be cast off into the blood stream as "blood histiocytes." The majority of the blood histiocytes are filtered out in the capillaries of the lung, where they disintegrate, and only a few of them reach the peripheral blood. Mass production of blood histiocytes may occasionally lead to a flooding of the peripheral blood by large phagocytosing mononuclear cells (endocarditis lenta, smallpox, malaria, kala-azar, septic reticulosis, etc.). The histologic analysis of a great number of cases of leukemia has convinced me that leukemia is characterized by the acquisition of blood cell-forming potencies by the entire mesenchyma, in particular the reticulo-endothelium and the fibrocytes. The power of differentiation into blood cells may be so strong that the reticulo-endothelial cells and fibrocytes reveal the structure of young blood cells while they are still sessile. Thus, in acute myelosis the Kupffer cells of the liver may be found filled with oxydase granules that extend into the branched processes. In a case of subacute myelosis with a predominance of eosinophilic myelocytes I have found the Kupffer cells stuffed with oxyphilic granules. In inflammatory granulation tissue in cases of myelosis I have seen neutrophilic and oxydase granules in the cytoplasm of swollen fibrocytes. In this premature differentiation of the sessile mesenchymatous cells the earliest stage of blood cell formation, namely that of the hemocytoblast, is skipped. In some cases of acute leukemia the mesenchymal cells develop into hemocytoblasts (stem cells) which enter the blood without further differentiation. These hemocytoblasts are often confused with lymphocytes.

The changes described are most striking in the cases of acute leukemia which take such a rapid course that the patient dies before the leukemic infiltrations have become too extensive to allow an analysis of the histogenesis. No matter what type of leukemia is diagnosed from the blood picture or what type of blood cell predominates in the lesions of the various organs, the leukemic formations always start in the same location.

So far as the relation between acute and chronic leukemia is concerned, I do not see any reason for considering them as two different diseases, as suggested by C. Sternberg, Gloor and others. Because of the slow development and prolonged course the histogenesis of the process is less distinct in the chronic leukemia than it is in the acute form. Because of the slow development there is also a greater difference in the distribution of the leukemic infiltrations than in the cases with rapid course. Fundamentally, however, the process is the same, as shown in those instances in which a chronic leukemia terminates in an acute one.

Recent years have brought an extensive literature on a new type of leukemia first recognized by Reschad and Schilling more than twenty years ago. I refer to the monocytic leukemia. Though questioned by outstanding hematologists like Naegeli and Carl Sternberg, there is so much evidence in favor of a monocytic leukemia that its existence can no longer be denied (Forkner, Fowler, Foord, Parsons and Butt, Clough and many others). Of thirty cases of acute and subacute leukemia which I have studied during the last three years, six were of the monocytic type. Much confusion, however, has been created by including among the cases of monocytic leukemia those with excessive, systemic proliferation of the reticulo-endothelial cells or of the reticular cells only (aleukemia, subleukemia, leukemic reticulosis or reticulo-endotheliosis). I consider these conditions as septicemias with abundant reactive proliferation of the reticulo-endothelium (see also Krahn, Akiba, Terplan and others). The appearance of numerous, sometimes phagocytosing, histiocytes in the peripheral blood does not indicate any relation to

leukemia, since the blood histiocyte is not the precursor of the monocyte, but an abnormal fully mature blood cell. The immature precursor of the monocyte is the monoblast, and it is the monoblast that characterizes the monocytic leukemia. I agree with Forkner, who traces the monoblast to the same parenteral cell from which the other blood cells are derived. Since in all types of leukemia the reticulo-endothelium acquires blood cell-forming potencies, one should not use the term "leukemic reticulosis" or "leukemic reticulo-endotheliosis" as synonymous with "monocytic leukemia," as is frequently done.

A critical study of the pathology of leukemia leads to the conclusion that leukemia has just as many features in common with malignant neoplasms as it has differences from them. There are many observations pointing toward relations between leukemia and a variety of inciting injurious agents such as infections, poisons (benzene), roentgen rays, trauma and dietary deficiencies. These observations are too numerous to be merely incidental. On the other hand, it is only in rare instances that a leukemia develops following the causes quoted. Hence one is compelled to assume disposing congenital factors, an abnormal constitution of the mesenchyme. In this connection reports on the familial occurrence of leukemia are of great interest (Weiss and Thums, Brugger, Wolff, Vercelotti, Riccitelli, Sorrentino, S. Petri, V. Deutsch, Morawitz and others). For these reasons it appears advisable not to identify leukemia with malignant neoplasms, but to consider it as a definite and separate disease entity.

CLINICAL AND THERAPEUTIC ASPECTS. LLOYD F. CRAVER (by invitation).

Despite extensive clinical observations of leukemia in recent years, there is nothing essentially new in its treatment. These observations have been of value chiefly in bettering one's understanding of the scope of the disease and in improving the technic of treatment.

Emile Weil and Isch-Wall's statement that the appearance of gross leukemic infiltrations, which they term "tumors," of skin, bone or external lymph nodes in the course of chronic myeloid leukemia signifies the terminal stage is true in general, but there are exceptions.

Priapism is much more rare than is generally believed. In a series of over a hundred male patients with leukemias observed at Memorial Hospital it occurred in only one.

In recent years several authors have discussed the interesting question of the relationship between erythremia and leukemia. Parkes-Weber speaks of erythroleukemia.

Infectious mononucleosis is frequently mistaken for lymphatic leukemia. Bunnell's report shows that the heterophile antibody reaction may be of great use in the differential diagnosis of infectious mononucleosis. However, the worth of this test cannot be judged without further extensive trials. It seems possible that what produces infectious mononucleosis in one person may cause leukemia in another.

Splenocontraction induced by intramuscular injection of epinephrine hydrochloride is believed by some French workers to be of value in certain doubtful cases, as judged by the effect produced on the blood count.

In treatment, more particularly of myeloid leukemia, the nearer the white cell and differential counts are brought toward normal, the better and more lasting are the results.

Forkner's use of "relentless" doses of arsenic has served to recall attention to this agent.

Nemenow suggested preliminary irradiation of the kidneys so as to free them from leukemic deposits and thus lessen the retention of uric acid. Arendt and Gloor suggested diathermic treatment of the kidneys in order to increase the circulation of blood through them and thus increase their eliminative function.

Friedgood drew an interesting parallel between exophthalmic goiter and chronic lymphatic leukemia, and has tried using iodine in lymphatic leukemia, with some palliative results.

The value of transfusions in leukemia is questionable.

The hemorrhagic diathesis has been lessened in some cases by exposure to mild actinic rays, together with a high vitamin intake.

Infected wounds may be very troublesome in leukemic subjects. In several cases rapid healing has resulted from small doses, from 100 to 200 roentgens, of lightly filtered, low voltage x-rays.

The infiltrations that rather commonly appear about the eyelids or orbits in lymphatic leukemia may yield readily to small doses of x-rays.

Total Irradiation.—For a number of years certain clinicians have treated leukemia by irradiation of the entire body. Their methods have been two: (1) to remove the roentgen tube a sufficient distance from the patient's body so that the beam of x-rays will include all or the greater part of the body; (2) to expose in succession large fields until the entire body has been treated. In general, the results of total irradiation have been about on a par with those of the usual methods of local irradiation; sometimes the results in the blood count and the size of the spleen have been less satisfactory.

Beginning in May 1931 and continuing for two years, my associates and I tested a new method of total irradiation, known as the Heublein method. Patients were treated continuously, day and night, with very weak intensities of radiation from a tube operating at 185 kilovolts placed at a distance of from 5.4 to 7.3 meters from the patients. By this method we treated five persons with myeloid leukemia, twenty-seven with chronic lymphatic leukemia and nine with so-called lymphatic pseudoleukemia. Of these forty-one patients fifteen showed improvement, and up to August 1, 1933, were living 4.5 to 21 months after treatment was begun. Ten showed distinct palliation but succumbed to the disease in from 3.5 months to 2 years after treatment. Sixteen patients failed to show improvement. However, we were experimenting with an entirely new method, and we feel that the poor results were largely accounted for by errors in the dosage and in the selection of cases. There is no doubt that in many of the cases, particularly in those of the lymphatic group, the treatment gave results that were at least equal if not superior to those obtainable by local irradiation. Our impression is that myeloid leukemia does not do so well as lymphatic leukemia following total irradiation, although we treated only five patients with myeloid leukemia.

DISCUSSION

FRANCIS CARTER WOOD: I have been treating patients with leukemia for thirty years by a combination of x-rays, radium, arsenic and similar drugs without, it seems to me, very much improvement in the results. These patients may be divided into two classes: First, those with acute leukemia, which tends to become hemorrhagic, in whom as a rule no beneficial result comes from any type of treatment. They are made worse by irradiation; they are not regularly benefited by transfusion; arsenic is useless, and most of them die within a short time. There are exceptions, of course. I have seen a patient symptomatically cured for a number of months by transfusions, but the disease returned in an even more acute form. The second type are the patients with chronic leukemia, and of these the ones with the lymphatic type of leukemia may be divided into three groups radiologically: a small group who, with suitable doses of x-rays applied to the spleen and nodes, will live for a period of years. They are usually older patients, and in them conditions are very favorable. I have had a number live for six to nine years with very little x-ray therapy, just enough to keep the count down and to keep the nodes from causing discomfort. There is another type in whom the disease is fairly rapidly progressive, and in whom irradiation does very little, except to reduce the size of the spleen and nodes, but they die without any particular benefit. Between these lies a group in whom palliation for a year or two is often obtained. In the type with acute myelogenous leukemia no benefit is obtained. In the type with chronic myelogenous leukemia, despite the statement that no prolongation of life is obtained, an amelioration can be brought about with x-rays in many

cases, and when one sees a practically moribund patient get up and go back to work for two or three years it is difficult to understand why one should think life cannot be prolonged.

It is difficult to classify these patients. They vary greatly under different types of treatment, no matter whether arsenic, which Naegeli has strongly recommended lately, or x-rays, which most favor, are used. Most physicians do not like to get the leukocytes down to normal, because every once in a while they go far below normal, and the patient dies with pneumonia or some other infection.

It is wise to keep the patient thoroughly informed as to the dangers of even minor surgical operations and pulling of teeth, the latter often setting up an intractable hemorrhage which may lead to the death of the patient in days or weeks.

I have succeeded in getting two women through pregnancy by careful irradiation up to the time of delivery, but in young women irradiation sterilization should be done.

Benzene is a very poor drug. It often causes a hemorrhagic diathesis and multiple lesions of the skin, and is not employed in my clinic in the treatment of leukemia. Recently Kraemer of Philadelphia has tried the use of lead, and has reported good results in a few cases, but such reports have no general value, because patients vary, and each must be treated cautiously and individually. However, there may be something in this treatment in that the lead is phagocytosed and carried to the spleen and bone marrow, and possibly has a toxic effect on the cells, so that the amount of x-rays necessary is diminished.

NATHAN CHANDLER FOOT: You have seen and heard the evidence on both sides of the question for and against leukemia as a tumor, and you realize where the poor pedagogues stand in regard to this matter when it comes to teaching students what the condition may be. One might think of the disease as a scale or a gamut, and range at one end those conditions in which the blood stream is flooded with the atypical white cells and the blood-forming organs are abnormally active, and at the other end of the scale those definitely localized myeloblastic tumors which are disseminated very much like ordinary tumors insofar as they metastasize widely (chiefly to the bone) and fail to flood the circulation with white cells. In the middle of this scale would come those types in which both of these observations are made: the circulation is flooded, and subsidiary tumors or infiltrations are formed. I think these daughter growths are not always so well borne as Dr. Jaffé's reference to Naegeli would indicate, for, particularly in chloroma in which one sees subsidiary tumors of a green color throughout the body, a good deal of damage to tissue results, and this is also indicated in what has been said concerning the kidneys.

One might make a similar scale in connection with leukemias of the lymphoid type, and then from this pass on quite naturally to those of the monocytic type. The chief stumbling block in the attempt to draw analogies between malignant tumors and the leukemias is this: One is trying to compare two pictures that are, from the histologic and physiologic standpoint, so fundamentally different under normal conditions that one is bound to fail if one pursues the attempt too closely. The blood is the most ubiquitous and labile of all the body tissues. One can get along fairly well with the analogy up to a certain point, but the normal and rapid circulation of the blood as a tissue is without analogy, and therefore a tumor of such a tissue is in a class by itself. Malignant tumors may use the blood stream as a means of transportation for their daughter cells, they themselves remaining fixed; in the leukemias, the tumor is an integral part of the moving vehicle itself; therefore if one merely attempts to adjust one's conception of malignant tumors of fixed tissues to the conception of a tumor in which the component cells are constantly being shuffled in a shifting and moving tissue, one will find the comparison not so fantastic as one at first conceived it to be.

That the cells of such a tumor may arise anywhere in the body as a development of Maximow's polyblasts may or may not be a fact; it still is under lively dispute, and, alluring as this theory may be, as one grows older and more cautious, one is less inclined to accept it unless its validity is conclusively proved by obser-

vations in vivo. The mere presence of oxyphilic or other granules common to granulocytes in cells that are notoriously avid phagocytes cannot be accepted as proof of their transformation into granulocytes. The theory is well worth investigating, and one must strive to maintain an open and unbiased attitude toward such questions. Maximow maintained that there is a supply of polyblasts throughout the body, cells that are mesenchymal in origin and that never reach a fixed condition of differentiation. They constitute, so to speak, a reserve force of persisting embryonal tissue that has the capability of becoming differentiated into a number of other forms, such as blood cells, if the occasion arises. They may form histiocytes, fibroblasts, lymphocytes and so on, and under certain circumstances, according to Maximow, the process may be reversed, the differentiated cell undergoing dedifferentiation and returning to the potential embryonal condition of the polyblast. Such a theory, while it is applicable within limits to inflammation and repair, becomes absurd if it is pursued to its logical conclusion. Mesodermal tissue can also produce epithelium, and as a result of this one finds some authors bold enough to derive epithelial tumors from these polyblasts and to explain the occurrence of cancer on such a basis.

Dr. Jaffé strikes a sympathetic note when he excludes the so-called aleukemic reticulosis from the leukemias. In a recent paper read before the New York Pathological Society I reported a case of that disorder and took the same stand on exactly the same grounds. To both of us the maturity of the monocytes in contrast with the immaturity of the leukemic cells and the almost invariable history of infectious disorders in connection with this disease prior to its development seemed very much against its being a leukemia. There are conditions in which the mononuclear cells may assume embryonal characteristics, such as generalized reticulosarcomatosis, and these are very different from the aleukemic reticulosis that Dr. Jaffé has mentioned.

This leads to the theory that infection is the cause of leukemia. Infections do call out large numbers of polymorphonuclear leukocytes in cases of ordinary leukocytosis. Many of these leukocytes may be of an immature type, a fact of some importance to the hematologist. One may see histologic pictures closely resembling leukemia of the myeloid type in the tissues of children who have died from acute infectious diseases, such as diphtheria and scarlet fever, with extensive myelocytic and even myeloblastic infiltrations of various organs. Ignorant of the clinical histories in such cases, one might be misled to diagnose the condition as myeloid leukemia, which would be quite erroneous.

The popularity of the old terms "acute leukemia" and "chronic leukemia" is bound to wane the more investigators work along the experimental pathways followed by Dr. Richter and Dr. Furth, for the more one knows about this disorder the less one is inclined to regard it as an inflammation to which the terms "subacute," "chronic" or "acute" may be applied. It is rather a question of the degree of malignancy as one sees malignancy illustrated in carcinomas—it may wax or wane in leukemia just as it may in neoplasms. Although I am not an enthusiast for the grading of tumors, one might grade the leukemias in some such fashion, having grades 1, 2 and 3 according to the rapidity of the growth, the extensiveness of the infiltration and so on.

NATHAN ROSENTHAL: Leukemia presents marked variations with respect to the symptoms, course and blood picture. The symptoms alone cannot be relied on for the diagnosis, which must rest on the characteristic blood changes. These do not depend on the number of white blood cells so much as on the presence and persistence of specific types of cells, such as myelocytes, myeloblasts and a relative and absolute lymphocytosis and monocytosis. It is interesting to note that the frequencies of the three main types of leukemia—myelogenous, lymphoid and monocytic—correspond with the percentages of the three main types of leukocytes in the circulating blood. The underlying systemic disorders are essentially the same in all cases, and their neoplastic or malignant character is evident. Further arbitrary divisions of the cases can be made according to the duration of the disease, acute or chronic, and according to the number of white blood cells, mainly

leukopenic or leukocythemic. In other words, the white blood cells in leukemia may vary from 400 to 1,000,000 in number.

The transmission of the disease in animals is an interesting problem. So far there is no information with respect to its transmission in man. I have observed this possibility in two patients as the result of blood transfusions from patients with polycythemia to patients with severe anemia in whom the leukocytes were not abnormal. In both patients, about a year after many transfusions were given, acute myeloblastic leukemia developed. This may indicate the close relationship of polycythemia and leukemia. In fact, leukemia is not infrequently the end-stage of polycythemia.

The treatment of leukemia is largely symptomatic. Arsenic, transfusions and particularly roentgen ray irradiation are the chief means of inducing symptomatic improvement, remission or possibly prolongation of life. Persons with acute leukemia may also be irradiated. In two such patients remissions were induced similar to those obtained in patients with chronic leukemia. No ill effects have been noted in the treatment of a large number of patients with acute leukemia.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, March 8, 1934

MORTON MCCUTCHEON, *President, in the Chair*

TENTH-NORMAL HYDROCHLORIC ACID AS A DILUTING FLUID FOR COMBINED LEUKOCYTE AND HEMOGLOBIN DETERMINATIONS. C. A. PONS and WILLIAM P. BELK.

With the use of the Haden-Hausser hemoglobinometer, for which a 1 : 20 dilution of blood in tenth-normal hydrochloric acid is made in a white cell pipet, an economy of apparatus and time would result if the white cells could be determined on the same preparation. Fifty-eight duplicate counts were made with tenth-normal hydrochloric acid and 0.5 per cent acetic acid. Counts on leukocytosis and lymphocytosis as well as on normal blood were included. In the hydrochloric acid preparations there was a slightly brownish background and the cells were smaller than in acetic acid. These differences were not sufficient to interfere with accurate counting. The average deviation of the two series was 6.09 per cent, the counts on the hydrochloric acid preparations being somewhat lower. However, when ten hydrochloric acid preparations were recounted after an interval of two hours, the second counts averaged 8.7 per cent higher than the first ones. This indicates that the white cells are preserved in this diluent for that period of time. A few observations on the distribution of the cells in the counting chamber with both diluents indicate that this factor alone may account for such differences as appear in the two series. Granted that a 10 per cent variation is permissible in the enumeration of white cells, tenth-normal hydrochloric acid appears to give accurate results.

EXPERIENCES IN EVALUATION OF THE GRUSKIN SKIN TEST FOR CANCER. JOSEPH MCFARLAND, M. FRIEDMAN and J. H. CLARK.

The Gruskin skin test for cancer was performed on 174 persons in the Philadelphia General Hospital. The antigen, prepared from the liver of fetal calves, was supplied either by Dr. Gruskin or by Sharpe and Dohme, Philadelphia, who prepared it under his direction. In all, 17 antigens were used. The patients tested were divided into two groups. Group 1 (controls) totaled 71 persons; 13 were presumably normal nurses or physicians; 48 presented 24 common diseases, not malignant; 10 complained of tumors, not cancerous (fibro-adenoma, Hodgkin's disease, giant cell tumors, osteoma, etc.). In this group 85 tests were performed,

yielding negative results in 74.1 per cent. Group 2 included 103 patients suffering from cancer, diagnosed by biopsy in 57 instances and clinically in 44; 114 tests were performed. The results were as follows:

	Cases	Results of Gruskin Tests: Positive	Results of Gruskin Tests: Negative	Tests	Per Cent Positive
Carcinoma (diagnosed by biopsy)					
Irradiated	32	28	6	34	82.3
Nonirradiated	27	22	10	32	68.7
Carcinoma (diagnosed clinically by x-ray picture, etc.)					
Irradiated	24	18	8	26	69.2
Nonirradiated	20	18	4	22	81.8
Totals	103	86	28	114	75.4

The results of the total series of tests were as follows:

	Cases	Tests	Results	Per Cent Accurate
Controls	71	85	Negative 63	74.1
Carcinomas	103	114	Positive 86	75.4
Totals	174	199	149	74.8

Our impressions of the test are: 1. It is based on a false immunologic premise; i. e., that an autochthonous growth of cells, possibly fetal in origin, certainly human in type ontogenetically, will produce a sensitivity in the fixed tissue cells to a phylogenetically foreign protein of embryonal type. 2. It is not and probably cannot be sufficiently well standardized to prevent conflicting results. 3. The reactions are indefinite and extremely hard to read. 4. The reactions are not typical of true allergy. 5. In no case was a cancer diagnosed by the test that could not have been recognized by more simple means.

THE RELATIONSHIP BETWEEN RHEUMATIC AND SUBACUTE BACTERIAL ENDOCARDITIS. WILLIAM C. VON GLAHN and ALWIN M. PAPPENHEIMER, Columbia University.

A series of twenty-six cases of subacute bacterial endocarditis was studied in order to make clear the relation between the underlying rheumatic disease and the bacterial infection. Histologic evidence of coincident active rheumatic lesions in the form of fresh verrucae was found in every case. In several instances, rheumatic vegetations free from demonstrable bacteria were present on valves unaffected by the bacterial infection. The incidence of Aschoff bodies in the myocardium was the same as in cases of uncomplicated rheumatic carditis. The more plausible inference from these observations is that, in the rheumatic subject, the subacute bacterial infection of the valves is implanted on active rheumatic vegetations.

RETOTHELIAL (RETICULO-ENDOTHELIAL) SARCOMA. R. PHILIP CUSTER.

Six cases of malignant tumors arising in cells of the reticulo-endothelial system are presented. From this material and published cases of others the following points are emphasized:

The predominant incidence is in the fifth and sixth decades of life.

The characteristic clinical features are: regional pain, a febrile course and moderate anemia, with progressive loss of weight and terminal cachexia.

The predominant site of origin is in the lymph nodes or the spleen. An occasional primary focus is in the pharynx or along the gastro-intestinal tract.

Propagation is by direct extension, lymphatic permeation and/or blood stream metastasis.

The duration is relatively short; in the group studied it was from five to twenty months following the onset of symptoms. The duration of one case was forty-

one months, but the sarcomatous condition was preceded by intestinal tuberculosis (demonstrated by laparotomy), and the onset of the tumor was indefinite.

The histologic criteria for diagnosis are: polymorphism of cells with morphologic evidence of their histiocytic nature, i. e., clear vesicular nuclei, abundant cytoplasm with vacuolation, delicate processes and phagocytic quality, and tendency to form mononucleated and multinucleated giant cells; occasional appearance of myeloid metaplasia within the tumor, and, finally, transitional forms between reticular and endothelial cells and tumor cells, the latter demonstrable in early cases before the entire architecture of the lymph node is lost.

The differentiation from lymphosarcoma and from multiform spongioblastoma is based on clinical and histologic grounds. Differentiation must be made from leukemic and aleukemic reticulosis (reticulo-endotheliosis).

It is recommended that pathologists adopt the term "retothelial sarcoma" (*Retothelsarkom*—Roulet) to serve for the terms "reticulum-cell sarcoma," "reticulum-cell lymphosarcoma" and "Hodgkin's sarcoma."

Regular Meeting, April 12, 1934

MORTON MCCUTCHEON, *President, in the Chair*

The William Wood Gerhard Gold Medal of the society was presented to Dr. George H. Whipple, after which Dr. Whipple gave the Annual Conversational Lecture, his subject being: "Regeneration of Hemoglobin and of Blood Plasma Proteins Controlled by Diet Factors."

Regular Meeting, May 10, 1934

MORTON MCCUTCHEON, *President, in the Chair*

CERTAIN FEATURES OF ARTERIOSCLEROSIS IN WILD ANIMALS. HERBERT FOX.

It has been possible by a combination of the Gömöri silver photographic method and the Spalteholz translucency method to obtain specimens in which a black precipitate is deposited in the areas that appear to contain calcium when sectioned and stained by hematoxylin and alizarin. Attention is directed to the provisions by Gömöri that this silver precipitation may not penetrate the entire mass but be limited to a narrow rim around such degenerations.

Incineration of arteries by the Policard method has added little to knowledge of the anatomy of vessels and the lesions of arteriosclerosis. Fibrillary thickening of the intima is accompanied by a striated ash. Atheroma of the intima shows a finely stippled ash. The ash of the media follows the lines of the elastica. The ash of the avian intima is coarser than that of the mammalian; this is consistent with the character of the elastica as shown by Weigert's stain in the two kinds of vessels. Heavy calcification shows a brilliant silver ash.

One feature of comparative arteriosclerosis may assist in forming an opinion about Thoma's theory in certain cases of bovine and psittacine arteriosclerosis: There is definite evidence that muscle degenerates before elastica, and that the elastic tissue and the whole wall may give way; the thickening of the intima may be for the purpose of retaining the lumen.

THE RESULTS OF THE STUDY OF SWINE INFLUENZA AND THEIR POSSIBLE APPLICATION TO THE HUMAN DISEASE. RICHARD E. SHOPE, Rockefeller Institute, Princeton, N. J.

Swine influenza is a disease which supposedly appeared for the first time in the fall of 1918 coincident with the great pandemic of human influenza. The disease has a sudden onset and is highly contagious. The salient clinical features

are fever, anorexia, extreme prostration, cough, a rapid diaphragmatic type of respiration and leukopenia. The mortality ranges from 1 to 15 per cent, death or recovery occurring after from two to six days of illness. The disease is readily transmissible from pig to pig either by contact or by intranasal inoculation with suspensions of infected lung or exudate from the respiratory tract of a sick animal.

The pathologic picture seen in animals killed on the second to the fourth day of illness is essentially that of an exudative bronchitis and massive lobar or lobular pulmonary atelectasis. The bronchi and bronchioles are filled with an exudate of polymorphonuclear leukocytes; the bronchial epithelium is fragmented or desquamated, and there is a peribronchial round cell infiltration. The alveolar walls are wrinkled, thickened and infiltrated by round cells. In fatal cases there frequently is an intensely edematous type of pneumonia.

The disease has been shown to be caused by the combined action of a filtrable virus and a hemoglobinophilic bacterium, Haemophilus influenzae-suis. Animals infected with the virus alone show an extremely mild and scarcely recognizable illness. Animals inoculated intranasally with pure cultures of H. influenzae-suis do not become ill and show no pathologic alteration at autopsy.

A comparison of what is known concerning swine influenza with the better known facts about human epidemic influenza indicates certain suggestive analogies between the two diseases. Taking into account differences in the anatomic and physiologic make-up of hogs and man, the clinical picture of the swine disease is strikingly similar to that of influenza in man; pathologically, fatal cases of the swine disease are strongly reminiscent of corresponding cases of the human disease. A hemoglobinophilic bacterium is prominently associated with both, and the organism encountered in the swine disease could not regularly be distinguished with certainty from that found associated with the human disease. The swine organism, H. influenzae-suis, is known to be etiologically essential to the production of the disease; the rôle played by the human organism, H. influenzae, is highly controversial.

Recently Smith, Andrewes and Laidlaw (Smith, Wilson; Andrewes, C. H., and Laidlaw, P. P.: Lancet **2**:66, 1933) obtained from persons with influenza a virus that is pathogenic for ferrets. Indirect experimental evidence strongly suggests that this virus is of etiologic significance. They furthermore observed that the swine influenza virus was also pathogenic for ferrets and produced a disease in these animals that was not only similar to that produced by the human virus but appeared to confer some cross-immunity to the human virus.

Since in swine influenza both the filtrable virus and H. influenzae-suis are known to be etiologically essential, an interesting possibility, made very apparent in considering features of similarity between swine and human influenza, is that the human disease may likewise have a two factor etiology: the virus of Smith, Andrewes and Laidlaw and H. influenzae.

Books Received

DIE HORMONFORSCHUNG UND IHRE METHODEN. Max Reiss, Dr. Med., Dr. rer. nat., Privatdozent für pathologische Physiologie an der Deutschen Universität in Prag. Price, 15 marks. Pp. 415, with 26 text figures. Berlin and Vienna: Urban & Schwarzenberg, 1934.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. VOLUME X. INFLUENZA (PART II), WITH SPECIAL REFERENCE TO THE COMPLICATIONS AND SEQUELAE, BACTERIOLOGY OF INFLUENZAL PNEUMONIA, PATHOLOGY, EPIDEMIOLOGICAL DATA, PREVENTION AND TREATMENT. D. and R. Thomson. Price, $17.50. Pp. 1557. Baltimore: Williams & Wilkins Company, 1934.

PROCEEDINGS OF THE PATHOLOGICAL SOCIETY OF PHILADELPHIA. NEW SERIES, VOLUME XXXI; OLD SERIES, VOLUME XLIX. Containing the transactions of the Society from January 1931 to January 1934. Edited by Herbert L. Ratcliffe, Sc.D., Secretary-Treasurer and Recorder. Philadelphia, 1934.

ARBEITEN AUS DEM SERO-BAKTERIOLOGISCHEN INSTITUT DER UNIVERSITÄT HELSINKI (HELSINGFORS). Herausgegeben von Prof. Dr. Osw. Streng. Band VI (1933-1934). Helsingfors, 1934.

AMERICAN TYPE CULTURE COLLECTION CATALOGUE OF CULTURES, 1934. Edition 3. Pp. 80. Chicago: John McCormick Institute for Infectious Diseases, 1934.

BIDRAG TIL SPØRGSMAALET OM RELATIONEN MELLEM B-VITAMINERNE OG ERNAERINGENS INHOLD AF PROTEIN, FEDT OG KULHYDRAT. WITH AN ENGLISH SUMMARY. P. Vogt-Møller, Reservelage ved St. Elisabeth's Hospitals Medicinske Afdelning, København. Pp. 165. Copenhagen: Levin & Munksgaard, 1934.

PHYSIOLOGY IN HEALTH AND DISEASE. Carl J. Wiggers, M.D., Professor of Physiology in the Western Reserve University School of Medicine, Cleveland. Price, $9. Pp. 1184, with 182 engravings. Philadelphia: Lea & Febiger, 1934.

AMEBIASIS AND AMEBIC DYSENTERY. Charles F. Craig, M.D., M.A. (Hon. Yale), F.A.C.P., F.A.C.S., Colonel, United States Army, retired; D.S.M.; Professor of Tropical Medicine and Head of the Department of Tropical Medicine, Tulane University of Louisiana School of Medicine, New Orleans; formerly Commandant, Army Medical School, and Director of the Department of Clinical Pathology and Preventive Medicine and Assistant Commandant, Army Medical Center, Washington, D. C. Price, $5. Pp. 315, with 54 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

Book Reviews

Diseases Peculiar to Civilized Man: Clinical Management and Surgical Treatment. By George Crile, M.D. Edited by Amy Rowland. Price, $5. Pp. 427, with 41 illustrations. New York: The Macmillan Company, 1934.

This book is based on the assumption that so-called neurocirculatory asthenia, hyperthyroidism, peptic ulcer, diabetes and epilepsy are related diseases. These diseases are assumed to result from disturbances of the glandular and autonomic nervous systems caused by the "tension" of highly civilized life.

The first part is devoted to the elaboration of the fundamental assumption that the diseases just mentioned are the direct outcome of civilized life. Arguments are advanced from the fields of phylogeny and ontogeny. The hypothesis of orthogenesis is invoked. According to this hypothesis, a tendency of protoplasm to develop in a certain direction, once set, cannot be arrested, but may continue to the great injury and even extinction of the species. The extinction of certain dinosaurs has been explained according to this notion as caused by the great size of the body and the weight of the armor, and the Irish elk is assumed to have been destroyed through the overgrowth of its antlers. And now the human species is assumed to be on the way to "hyperkineticism," due to an excessive evolution of the energy-transforming system which includes the brain, the thyroid, the suprarenals and the sympathetic nerves. The "kinetic diseases"—neurocirculatory asthenia, hyperthyroidism, peptic ulcer, etc.—are assumed to be the outcome of the racial physiology peculiar to the rise of man in civilization and to affect especially persons of outstanding intellectual and emotional qualities. In the course of the discussion of these assumptions statements are made that arouse doubt. Here is one: African natives do not have peptic ulcers, nor do morons, because they are sheltered from the worries of civilized man. It is also suggested without adequate basis that the diseases in question, at least in part, are of comparatively recent origin. In fact, is the assumption that there is a hyperdevelopment of the "energy system" peculiar to civilized man justified? The author does not hesitate to follow his assumptions confidently to the limit: "Since all parts of the brain-thyroid-adrenal-sympathetic system are involved in the hyperactivity which produces these diseases [neurocirculatory asthenia, etc.], it is obvious that treatment may include only one point of attack or more than one, the objective in each case being to lessen the factors that are causing the damaging kinetic drive. Thus they may be treated by lessening the driving power of the brain by rationalization, or by excision of the sympathetic ganglia; by lessening the driving power of the thyroid gland by thyroidectomy or by interference with its sympathetic nerve supply by ligations; by lessening the driving power of the adrenals by denervation; or in certain cases certain of these procedures may be combined."

The second part describes in some detail "the diseases of civilized man," particularly so-called neurocirculatory asthenia, which, in spite of all that is stated about it, does not stand forth as a definite and distinct clinical or etiologic entity. The third part deals with matters of surgical technic, and the fourth part, the longest, contains histories of cases. Finally comes a general summary.

In the part relating to treatment the main emphasis is laid on operations on the suprarenal, the "brain" of the sympathetic system. Eventual suprarenal denervation became the routine treatment for patients with so-called neurocirculatory asthenia and "has been used successfully in the treatment of recurrent hyperthyroidism and of certain cases of primary hyperthyroidism, in the treatment of a limited series of cases of diabetes." The operation has proved of value also in certain cases of epilepsy. But the evidence is not in any sense convincingly in favor of the operation. There are no series of control cases. The influence of other factors besides the operation is not considered. No study has been made of the

structural changes following the operation. Is the "cut in the lines of communication" permanent? There is, in fact, no evidence adduced to show that suprarenal denervation interferes with suprarenal function.

This is a book of unfounded and unverifiable assumptions. That human beings are experiencing hyperkineticism from the excessive evolution of the energy-transforming system is an assumption. That so-called neurocirculatory asthenia, hyperthyroidism, peptic ulcer, diabetes and epilepsy are caused by hyperactivity of the kinetic system is also an assumption. That suprarenal denervation or other operations assumed to be "dekineticizing" cure these diseases or any of them is another assumption.

No consideration is given to the constant tendency in nature toward balance or equilibrium or to Cannon's conception of homeostasis, which sets forth the idea that any tendency toward change is met by increased effectiveness of the factor or factors which resist the change.

Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms. By Priv.-Doz. Dr. Heinrich Westhues, erster Oberarzt der chirurgischen Universitäts-Klinik, Erlangen. With an introduction by Prof. Dr. Schmieden, Frankfort-on-Main. Price, 29.50 marks. Pp. 113, with 107 illustrations. Leipzig: Georg Thieme, 1934.

This small book of 113 pages is a valuable and authoritative contribution. It is in large part a study of rectal polyps and their relation to cancer. It is liberally illustrated with reproductions of specimens and photomicrographs, many of which are in color; a full bibliography is appended.

The author has had the opportunity to investigate much clinical material, and judging from his description of his gross specimens he has been painstaking in his investigations. He approaches the subject as a surgeon with sound basic training; more than three fourths of the book is devoted to the pathologic anatomy of the disease. He classifies rectal polyps into three groups, as has been done by others, but his classification is his own. It is based on the degree of cell differentiation and the general structure of the gland tracts. He emphasizes the clinical application of this classification. In group 1 are the purely benign polyps. In group 2 are those in which a progressively spreading epithelial variation occurs; while most grow to a good size without malignant changes, they eventually become malignant in a large number of cases. Group 3 is made up of growths with marked atypical epithelial changes, many of which are carcinomatous. Pea-sized carcinomatous polyps are not infrequent. The book is divided into three sections: first, that on the structure of rectal polyps; second, that on the growth and local distribution of carcinoma of the rectum, and third, that on the clinical application of the study. In the first section the author states: "I determined that in about 45 per cent of all rectal carcinomas, the origin from polyps is highly probable. Together with a previously mentioned 15 per cent of absolutely certain cases, we can state, therefore, that about 60 per cent of all cases can be proved or determined as highly probably of polyp origin." In the second section it is pointed out that local metastases occur from below upward, that they are practically never below the rectal growth (excluding, of course, anal carcinoma). In the last section it is emphasized that rectal fixation in itself is not a contraindication to operation and that conclusions as to either local metastases or metatases to the liver cannot be drawn from the size of the growth. The demands of complete (radical) resection of the rectum for cancer are fulfilled by excision of the bowel 2 cm. above and below the growth and removal of all perirectal connective tissue and fat at its level and from 10 to 12 cm. above it. If polyps are present, as they often are, the polyp-bearing area is excised, if this can be safely done. The author emphasizes again that most rectal cancers develop from polyps and that the majority of polyps become malignant. The book merits the attention of pathologists and is a worthy guide to the surgeon.

A Textbook of Histology. By Harvey Ernest Jordan, A.M., Ph.D., Professor of Histology and Embryology, University of Virginia. Sixth edition. Cloth. Price, $7.50. Pp. 738, with 610 illustrations. New York & London: D. Appleton-Century Company, Inc., 1934.

This is a standard and well established textbook of histology. The first edition was published in 1916. In this edition the text has been revised and in part rewritten. The sections that have received most attention in the revision are, according to the preface, those dealing with the blood, the reticulo-endothelial system, the endocrine glands, the striped muscles, the neuroglia, the nerve tissue, the reproductive organs and the lymphoid organs. However, the book has not been increased in size over that of previous editions. New illustrations have been introduced, and the book is suitably and richly illustrated. The style is clear and orderly. The functions of various structures are described briefly. The work merits the popularity that it has attained.